Contributions to the pathophysiology and treatment of varicoceles

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Contributions to the pathophysiology and treatment of varicoceles

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te verdedigen door Peter Vanlangenhove

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Voor Anne-Rose, Sim, Cas, Ko en Lie

The only source of knowledge is experience.

(Albert Einstein)

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1 Introduction

1 Introduction

History

In my final year of secondary school, I was still hesitating about what I wanted to become. I was quite sporty and I was not a bad football player. According to my father, unfortunately, I had the wrong character to become a professional sportsman. Therefore I decided to go for a master degree in "Lichamelijke opvoeding". My father, a general practitioner, was not so excited about my choice and tried to convince me to become a medical doctor. He argued that one could pave the streets with guys who obtained a master degree in "Lichamelijke opvoeding". Determined and stubborn as I am, I took the train to Ghent and for some unknown reason I enrolled for Medicine anyway.

I never regretted this unexpected and impulsive choice during my student years in Ghent, on the contrary. But in the last year of medicine I had to make another important choice; to become a GP or a specialist. To become a GP, seemed to be the obvious choice, certainly for my parents. Student life in Ghent was quite a contrast to the rough life of a GP in beautiful but rural Meulebeke. If I started the training as a specialist in Radiology, I would be able to continue my live in the exciting city of Ghent. Moreover, Radiology seemed to me a peaceful nine to five job far away from nagging patients. It was well-known that Radiology was one of the best-paid specializations, and that made the picture perfect for me.

Against my expectations, during my Radiology training at the Ghent University Hospital, the pure picture protocolling work became less exciting. Little by little my need for more patient contact increased. Therefore, I was lucky that the department of Radiology detached me as the first assistant ever to the Ultrasound department. Professor Voet introduced me into the world of color Doppler ultrasound. Dynamic imaging of the veins became my field of interest. It was a challenge to explore a so far neglected but exciting new domain.
In the department of Radiology, the catheterization of blood vessels and performing interventions were my cup of tea. I promptly requested an extension of my training period in angiography. Training was hard but moral was kept high by the enthusiasm of the assisting nurses and technicians. The nurses, of whom one is still working at the VINRAD department at the UZGent (Roos Dewulf) were eager to show me the dark rooms of Radiology where at that time the tormenting translumbar aortofemorography in Room 11 was still common practice. From Room 11, I ended up in Room 13. In Room 13, Professor Kunnen used a refined coaxial catheter technique to embolize varicoceles with glue. To me it felt as I went from the prehistory of Interventional Radiology to its unexplored bright future.

And then 1993, Defreyne arrived. After one week, it was clear to me that the ever aspired nine to five job completely belonged to the past and instead a whole new world of selective catheterizations, dilatations and embolizations opened up to me.

Fig 1: An example of a truss and a suspender, which were applied during several months, to achieve an involution of the varicocele.

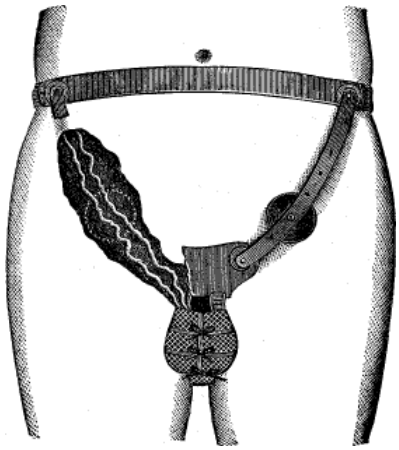
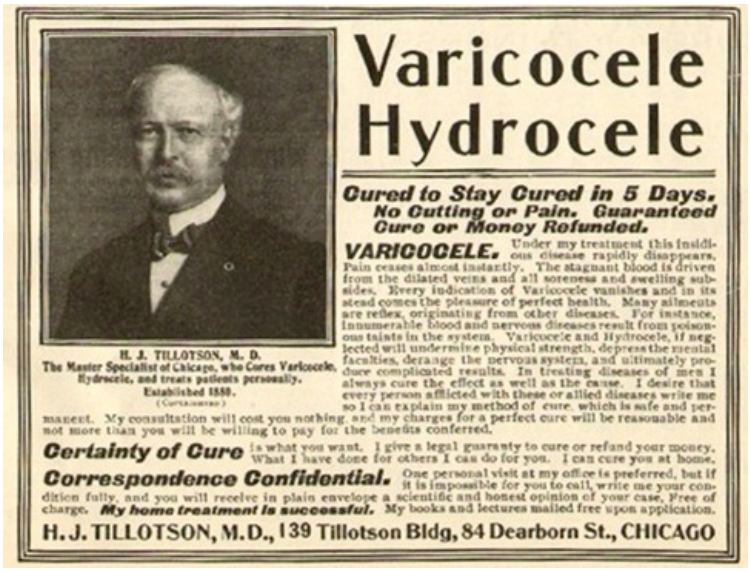


Fig 2: Public promotions for varicocele treatment were not rare in the 19th century.



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VARICOCELE. Under my treatment this insidious disease rapidly disappears. Pain ceases almost instantly. The stagnant blood is driven from the dilated veins and all soreness and swelling subsides. Every indication of Varicocele vanishes and in its stead comes the pleasure of perfect health. Many ailments are reflex, originating from other diseases. For instance, innumerable blood and nervous diseases result from poisonous taints in the system. Varicocele and Hydrocele, if neglected will undermine physical strength, depress the mental faculties, derange the nervous system, and ultimately produce complicated results. In treating diseases of men I always cure the effect as well as the cause. I desire that every person afflicted with these or allied diseases write me so I can explain my method of cure, which is safe and permanent. My consultation will cost you nothing, and my charges for a perfect cure will be reasonable and not more than you will be willing to pay for the benefits conferred.

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VARICOCELE.

MASTER SPECIALIST

The Disease An enlargement of the veins of the scrotum, giving it a knotted or swollen appearance of the scrotum most frequently.

Its Cause Often indigestion, but sometimes blows, falls, strains, excessive horseback or bicycle riding or excessive gratification.

Its Effect A dull, heavy, dragging pain in region of back, or body and brain, nervous debility, partial or complete loss of vigor and often failure of general health.

Its Cure All victim of Varicocele, come to our office and let us explain to you our process of curing it. You will then not wonder that I have cured to stay cured hundreds of cases of Varicocele, Hydrocele, Contagious Blood Poison, Stricture, Weakness, Nervousness in the very beginning. All our methods reduce soreness and swelling quickly patients. The roots of stagnant blood are forced from the dilated veins, inflammation and soreness are relieved from the start, the poisonous matter in the blood is eliminated entirely and forever, and in their stead comes the tide, the power, and the pleasures of perfect health and restored manhood.

We also Cure to Stay Cured Stricture, Nervo-Sexual Debility, Contagious Blood Poison, Rupture, Kidney and Urinary Diseases.

References: Best Banks and Leading Business Men of This City.

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What Defreyne performed in the arteries and Kunnen in the veins, has been a challenge for me ever since then.

As the only candidate, I applied for a residency in color Doppler ultrasound and Interventional Radiology. Professor Kunnen and Dr. Marc Mespreuve prepped me thoroughly to continue the embolization of varicoceles with glue at the Ghent University Hospital. They advised me not to change their optimized technique and repeated both "Don't use another embolic agent because glue is the best one!"

Meanwhile, I became more experienced in the technique of superselective embolization with glue in arterial bleedings (iatrogenic, traumatic, bronchial, gastrointestinal...). But also in the venous circulation (esophageal varices, portal vein, cavernous corpora...) all kind of vessels and leaks were occluded with glue. New mixtures with glue and new techniques with other liquids were investigated and tested in the veins in the veterinary medicine school in Liege at the Radiology department of Professor Snaps [(1)]. Also by giving presentations at meetings of the Section of Interventional Radiology, Ghent was automatically associated with 'glue'. In everyday work we became real 'glue adepts'. These experiences and investigations caused that varicoceles still are treated exclusively with glue since the departure of Professor Kunnen. I'm convinced that glue is still the best embolic agent for varicocele occlusion. Regarding the technique, I partially disregarded the good advice of my predecessors and I gradually adapted and extended the existing technique with new techniques I acquired during the arterial embolizations I performed.

Backgrounds

Idiopathic varicocele is usually the first physical abnormality encountered as a young adolescent [(2)]. You rarely have complaints, but when the School doctor announces it, you suddenly realize why you had to blow on your hand during all these years.
The earliest descriptions of varicoceles came from Aulus Cornelius Celsus, a Roman encyclopedist, who practiced from 25-35 AD. In the "De Medicina" he wrote
"*When the disease has spread over the testicle and its cord, the testicle sinks a little lower, and becomes smaller than its fellow, in as much as its nutrition has become defective*".
It lasted until the 16th century when Ambroïse Paré, the most celebrated surgeon of the Renaissance, recognized varicoceles as a clinical problem with pain and swelling. He attributed it to melancholic blood.
It was in 1843 that the British surgeon T.B. Curling introduced the term "varicocele" [(3)]. Several of his patients affected with varicoceles mentioned a considerable relief of pain while pressing with the fingers on the groin. He applied counterpressure with a truss and a suspender during several months and achieved an involution of the varicocele [(4)] (Fig 1). At the end of the 19th century, the treatment of varicocele was a hot topic in the Unites States and it was eagerly advertised (Fig 2).

Robson reported a complete scrotal excision of the varicocele in 1886 [(5)]. From the early 1900s, the scrotal approach had been abandoned because of high complication rates. In 1918 Ivanissevitch introduced surgical techniques, which are still the base of todays operative treatment. Important complications of surgery such as hydrocele, infections, epididymitis, haemorrhage and loss of functioning testis induced reluctance to treat varicoceles among surgeons. Charels Wells explained in 1948 the point of view of the British surgeons as follows:

"In civilian practice very little importance is attached to a varicocele. On the assumption that the condition is little more than an exaggeration of the normal with an added neurosis, reassurance and local support with a suspensory bandage may safely be advocated as the treatment in most cases."
Barfield, a British surgeon, first proposed a relationship between infertility and varicocele in the late 19th century. Through the early 1900s, reports by other surgeons continued to describe this association. Tulloch reported in 1951, sperm count improvement after varicocele repair in a biopsy proven azoospermic individual (i.e., without sperm) [(6)].
Thereafter, treatment indication shifted from pain relieve to restoration of fertility.

Varicocele is the most common correctable etiology of infertility in adult men. Adolescent varicocele was thought of minor clinical importance, until investigators confirmed a significant reduction in ipsilateral testicular volume. After varicocele correction, the volume of the ipsilateral testis increased significantly[(7)]. A number of surgical and endovascular treatments of varicoceles are available today.

With the rise of interventional radiology, it was quickly recognized that also non-surgical methods could be used to treat varicoceles.
Since then, all kinds of embolic agents (alcohol, hot contrast agents, balloons, coils and sclerosing agents) had been used worldwide. Ghent was the first to use glue.

In was in 1980 in this University hospital that Kunnen initiated the use of glue (Isobutyl-2-Cyanoacrylate (IBCA)) for the endovascular treatment of varicoceles [(8)]. Glue in contact with blood causes a polymerization and forms an immediate intravascular occlusion. The polymerization produces an exothermic reaction resulting in a limited thermal damage of the vessel. Degradation products cause an acute inflammatory reaction in the vessel wall and in the surrounding tissues, followed by a chronic inflammation, which finally results in fibrosis of the vessel [(9)] [(10)]

In 1985 IBCA was replaced by n-Butyl-2-Cyanoacrylate (NBCA) or Histoacryl® by reasons of possible carcinogenicity [(9)] [(11)] [(12)]. Despite excellent embolization results in varicoceles and in cerebral and peripheral arterial indications, NBCA never received a CE-label for intravascular use. The company Braun did never made an application.

In 2001, a new glue consisting of almost the same formula as NBCA came on the market as Glubran2 (NBCA-MS) [(13)]. NBCA-MS should have the same occlusive embolic capacities as NBCA, but would be less adhesive, more stable and less histotoxic and less inflammatory than NBCA. These characteristics could make the embolization procedure more controllable and the inflammatory pain reaction less pronounced [(14)]. The new glue seemed promising, certainly because NBCA-MS has a CE-approval for endovascular use.

In all these years, little fundamental research has been performed into the effectiveness and tolerance of glue.

As no study proved the superiority of the newer NBCA-MS over the classical NBCA in a clinical embolization setting, we were eager to test it. Moreover, we were challenged by a recent review article on varicocele embolization that merely declared that NBCA-MS is superior to classical NBCA [(15)].

Due to my long experience with NBCA in varicoceles, we chose the insufficient internal spermatic vein (ISV) as a model to compare both glues. We initiated a double-blinded (patient

and interventional radiologist) comparative prospective randomized study with both NBCAs to compare handling, safety and efficacy of each agent during embolization (**part** 1 1.1).
Controlled randomized blinded studies are rather exceptional in Interventional Radiology. Because we expected a high efficacy and occlusion rate of the ISV, we looked for additional parameters to assess and compare the handling of the glues. For each single embolization act, an "embolization plan" was conceived and notified to the nurse, who wrote it down. The plan depended on the anatomy of the ISV and described how the occlusion would be achieved in one single embolization act.
Safety of the tissue adhesive was evaluated by the stability and consistency of the embolus during and 10 minutes after embolization and by sticking of the tissue adhesive to the microcatheter.

Heye et al. reported that there was no evidence of a different pain sensation during varicocele embolization with NBCA-MS in comparison with NBCA [(16)]. However, in this study, the investigator was not blinded for the glue. The pain sensation was only evaluated at the end of the procedure by a VAS questionnaire. We believe that a continuous pain registration during the procedure could reflect more precisely what the patient feels. For that reason, we used a paper with fixed numeric scores related to hand movements in order not to interfere with the embolization act (**part** 1 1.2). Only adult patients were included in our study, to minimalize the subjective aspect of pain sensation. In the case of bilateral varicocele, the concomitant right spermatic vein insufficiency was treated with the concurrent NBCA, to check intra-patient consistency of pain reporting. Persisting or discomfort during one week after embolization was evaluated by a questionnaire at home, where patients could indicate their findings on a drawing.

During my residentship in Interventional Radiology, in 2000, I assisted at the first embolization of an intracranial-arteriovenous malformation (cAVM) with ONYX. Before that time, intracranial AVMs were embolized with glue.

Onyx (ethylene-vinylalcohol) is a plastic dissolved in dimethyl sulfoxide (DMSO), which can be pushed and extended in different directions in vessel structures. Today, we have replaced glue by Onyx for the embolization of cAVM and dAVF. Onyx proved to be superior to glue because it penetrates deeper and wider into the nidus of a cAVM or into the complex feeder network of the dAVF. The microcatheter will rarely stick to the vessel wall, because Onyx has less adhesive capacities than glue. Another advantage is that the embolization can be done slowly and controllable while performing control angiographies. Histopathology of resected AVM's that were partially embolized with Onyx, showed little inflammatory reaction at the vessel wall or in the surrounded tissues. This stood in contrast to specimen of glue-embolized AVM’s.

In certain varicoceles with complex anatomy and extensive collaterals, we observed a similar complex network like cAVM's. We thought that ONYX could offer a better chance to fill all those collaterals with one continuous injection. Moreover, since inflammation after Onyx embolization is low, we thought that the post-embolization discomfort we observed with glue could be reduced. We started a pilot study to investigate the feasibility, safety and tolerance of varicocele embolization with Onyx (**part** 1.1.3).
We handled Onyx in the same way as we did the embolization with glue. Discomfort and pain reaction during and in the week after embolization were registered with the same numeric pain scale and questionnaire as we used in the glue studies.

Percutaneous glue embolization has the advantage of being an outpatient procedure with a faster return to normal activities than surgery. However, catheterization and embolization requires the use of X-rays. Therefore, the radiation exposure must be kept as low as reasonably achievable (ALARA principle) [17].
Literature data on the radiation exposure during varicocele embolization is rather scarce. Reported associated radiation risk was found to be within the range of other X-ray diagnostic procedures[18-20]. All these results were based on effective dose calculations in a standard-sized mathematical model, which does not take into account the size of the treated patient. Moreover, the effective dose is not appropriate to quantify the radiation risk in an individual patient [17]. In particular, the effective dose for an individual male patient does not exist. A gender averaging procedure is to be carried out!

During varicocele embolization, we use radiation in the proximity of the testis, a highly sensitive organ not only in children but also in adults consulting for infertility. We were eager to find out whether the use of pulsed fluoroscopy increases radiation safety. A master thesis student in Biomedical Sciences, Jolien Debonne, promoted by Klaus Bacher, helped us to answer this question. We started a prospective study to measure exposure parameters (DAP, kVp, beam filtration) and skin and testicular doses (with thermoluminescent dosimeters) during varicocele embolizations (**part** 1.1.4).
To obtain accurate organ dose estimates, a patient-specific Monte-Carlo simulation was set up. As a result, a detailed overview of the radiation exposure during endovascular varicocele embolization procedures was obtained. Afterwards, organ doses were converted into a cancer risk.

Adolescents with a varicocele are treated to stop testicle volume lost and to preserve fertility. Prophylactic treatment is based on the assumption that varicocele in children is an early stage of the adult varicocele.
The adult varicocele is more often symptomatic. Most adult patients are referred for a sperm dysfunction and to increase the pregnancy chance. The number of adolescents and adults referred to our department is equally high.

At a certain moment in my practice, I had the impression that varicocele embolizations in adolescents, was a more straightforward procedure than in adults. I thought to see more competent outflow valves and a more complex anatomy of the ISV in adult patients. These observations could be an indication for a different phlebographic anatomy of the ISV in adolescents and adults. Such difference could disclose a different pathophysiology of varicoceles.
Wouter Devleeshouwer, a medical master thesis student, delivered a complete literature review on the embryogenesis and anatomy of the ISV and the association with varicocele. In his work, we didn't find any hints for a different etiology or pathophysiology between adults and adolescents.
To investigate whether our observations were relevant, we set up a blinded, retrospective study comparing major phlebographic radio-anatomical landmarks in both age groups (**part** 2.2.1.). Sofie Van Waesberghe finished this study as part of her master thesis, bringing all different parameters beautifully in context.
The radio-anatomical landmarks were based on phlebographic features of the right and left ISV. We also included relevant phlebographic classifications for the left (Bähren) and right (Siegel) varicocele. Phlebographies of 500 consecutive varicocele embolizations were anonymized. Patients from 17 to 24 years old were excluded to ensure two populations with either distinct adolescents or distinct adults.

A memorial day for all those interested in the pathophysiology of varicoceles was the doctoral thesis defense of the in Israel residing Dr. Gat, December 2006 at the UGent. In his publications, the theory of the hydrostatic pressure is pivotal. At the defense, Prof Oosterlinck, Urologist, asked the question whether this pressure has ever been measured in humans? The answer by Gat was clear and firm: No, you do not need to go from the earth to the moon to measure the distance between them. The promoter of my thesis had the fortune to witness these historical quotes.
Recently, in an editorial of Andrologia, Gat titled even more seriously that " Erect posture of humans leads to infertility. " [(21)].

In an erect position, insufficient valves cause blood reflux, resulting in a hydrostatic pressure that could arise above the arterial pressure at the testicle. Hydrostatic pressure is a critical component of microvascular fluid exchange and convective transport of essential hormones enables spermatogenesis. The increased pressure would also impair the cooling and draining system of the testicle, namely the PP. Toxic degradation products in the testis would not be sufficiently drained. Moreover, the hydrostatic pressure would interfere with the arterial and nutritional supply of the testicle and impair spermatogenesis and testicle growth.

According to Gat, this reflux and pressure suites the laws of hydrostatics and communicating vessels. Gat et al. claimed that increased pressure is only caused by the hydrostatic pressure, and thus directly determined by the distance (height) between the PP and the renal vein.

Where Gat presented his theory as a fait accompli, we at least had some reservations and we wanted to expose this theory to the test of experimentation. (**part** 2.2.2).

In a first study, pressures in the ISV were measured by means of an external pressure-sensitive sensor on the level of the right atrium and by an arterial pressure line in connection with the microcatheter. The initial results disproved completely the theory of hydrostatic pressure. Unfortunately, we found that our measurements were not reproducible. With Tom Vandenberghe and Patrick Galle, at that time the fixed spermatica team and both “practical guys”, I tried to find out where we went wrong.
On December 6th, Sint Defreyne came up with a brochure of a pressure wire. This dedicated guidewire was thoroughly tested and it became clear for us, the innocent idiots of hydrostatics, that the outer pressure measurement had to be positioned at the level of the tip of the microcatheter.
The basic stone of a standardized measurement method was laid. Later, with Ellen Delanghe, our study coordinator and biomedical mathematician and musician, I developed a set-up with an external pressure transducer set and a microcatheter achieving comparable and reproducible measurements. These transcatheter measurements proved to be compatible with the results obtained with pressure wires in vitro and in vivo.
Pressure measurements were performed in the supine 0° and semi-erect 45° position, in the renal vein and the ISV. And there we went, and after many measurements we were happy to find how to explain the way pressures behaved in the ISV. We contributed to the pathophysiology of the varicoceles, and corrected the theoretical enigma of Gat.

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2 Incidence, pathophysiology, diagnosis and treatment of varicoceles

Part 1 Incidence of varicoceles

Presentation, incidence and epidemiology of varicoceles.

The vast majority of adolescents with varicoceles are asymptomatic [1]. It may be an incidental finding, being discovered at a routine school medical examination.
An adult patient with a varicocele consults either for complaints or for infertility problems. A varicocele may cause scrotal pain or heaviness at the scrotal sac.

Approximately 15% of all men in the general population have a clinical varicocele. Very few reports of varicoceles have been published in domestic mammals. Varicoceles are rare in mammals, probably because evolutionary they kept on moving on hands and feet. Watt et al. (1978) described bilateral varicoceles in 2% of Merino rams. Other reports on mammalian varricoceles are not available.

In contrast, between 19–41% of men investigated for infertility have a varicocele [2]. The incidence of varicocele in men with secondary infertility rises to approximately 70% [3]. This observation suggests that with age, the impact of varicoceles on fertility becomes paramount. Because varicosis prevalence increases with advanced age, Canales et al. hypothesized that the incidence of varicoceles in the elderly population would be greater.
He detected a 42% (19.8% bilateral, 22% left varicocele and 1.1% right varicocele) prevalence of varicoceles in 354 elder men (mean age 60.7 years), which was greater than the prevalence in historical control younger populations [4]. These data suggest an increase of varicocele with age. The sudden development of varicocele in an older man may indicate a retroperitoneal tumor blocking the spermatic vein, although this is quite rare.

Varicoceles were less likely to be diagnosed among obese men [5, 6]. Nielson suggests that adiposity protects against the “nutcracker” phenomenon.
It was found that presence of peripheral varicose veins was independently and positively associated with varicocele [7].

In children and adolescents, a varicocele was detected in (7.2%) of 4052 boys by physical examination [8]. The prevalence was 0.79% in children aged 2-6 years, 0.96% at 7-10 years, 7.8% at 11-14 years and 14.1% at 15-19 years. The prevalence increased significantly at age 13 years, somewhere at the start of puberty. Varicoceles are rarely found in boys six to nine years of age [9] [10][8]. The incidence of varicocele reaches its maximum of 16% in boys after puberty [10].
Baeck et al. found in 1938 boys with a mean age of 14.1 years (range 13-16 years) a unilateral left and right varicocele in 15.2% and 0.4% respectively [5]. Bilateral varicoceles were found in 0.9% of the boys. The proportion of boys with testicular size discrepancies increased with the severity of the varicocele grade. 50% of the boys presented with a unilateral testicular hypotrophy [10].

Akbay et al. detected a significant prevalence increase with age and an increasing testicular atrophy with puberty. He concluded that varicocele is a progressive disease.

In one of our studies (**part** 2. 2.1), we compared phlebographic characteristics of varicoceles between adults and adolescents. The incidence of valve dysfunction, renospermatic bypasses and the nutcracker phenomenon was higher in adolescents than in adults. These findings are disconcordant with a purely evolutionary concept of the left-sided varicocele. On the right side however, the phlebographic diameter of the ISV, the number of medial collaterals and the

incidence of varicocele increase with age (14.7% in adolescents and 33% in adults), which could support the theory of a progressive disease.

The varicocele was unilateral in 89.7% of the boys, in which, one (0.38%) was on the right side and all the others on the left side. Varicoceles were bilateral in 10.8% aged 11-19 years but none were detected in those aged < 11 years [8]. Most studies based on venography and with large number of patients report a bilateral varicocele in 25% [11] [12] [13]. In studies using different diagnostic tools, bilateral varicocele was reported in a range between 40 % and 60% [14] [15]. Gat et al. questioned the fact that varicocele should be considered as a mainly left-sided disease. In reports on adolescents and infertile males, they detected a bilateral varicocele in more than 80% with venography [16].

The heredity of varicoceles and the potential transmission to first-degree relatives has been little investigated. Clinical varicoceles are more prevalent among first-degree relatives of patients with known varicoceles [17].
Raman et al reported a 8-fold greater incidence (56.5%) of a palpable varicocele in first-degree relatives of patients with a known varicocele (6.8%) [18]. In their investigation neither varicocele grade nor bilaterality was predictive of inheritance in first-degree relatives. The inheritance relation of varicoceles is particularly in brothers (36.2-55%) and less in son father relation (21-26%) [19] [20].
In daily practice, no recommendations are available regarding the counseling of the brothers or sons, of men with palpable varicocele. Since studies suggest a hereditary behavior of the disease, guidelines of screening for male family members could be edited. Men with undiagnosed varicocele could be at risk of impaired spermatogenesis and future infertility.

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Part 2 Pathophysiology, diagnosis and treatment of varicoceles

REVIEWS

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Pathophysiology, diagnosis and treatment of varicoceles: a review

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In this article we reviewed the pathophysiology, diagnosis and treatment of varicoceles. The etiology and pathogenesis of varicoceles cannot be explained by one theory. Valve dysfunction, ontogenetic collateral formation and the nutcracker phenomenon seem to act synergistically. Hyperthermia, elevated hydrostatic pressure and antisperm agents are suggested as possible causes for the pathophysiology how varicoceles induce infertility. However the combination of patient's lifestyle, genetic factors and the consequences of reflux into the pampiniform plexus are believed to contribute to the infertility. Although venography stays the gold standard, the combination of physical examination, color Doppler ultrasound and thermography has the highest sensitivity and specificity to diagnose a varicocele. Regarding infertility, we are still searching for strict criteria or grading, to decide which patients with a varicocele may or may not have benefit from treatment. Treatment of varicoceles can be performed by different open surgical or percutaneous techniques. Treatment of varicoceles for infertility or to prevent infertility remains controversial, because the majority of men with varicoceles are still fertile. At the moment, inguinal or subinguinal microscopic surgery gave the highest pregnancy rates, the lowest recurrence and lowest complication rates. But retrograde superselective glue embolization or sclerosing of the ISV are the best percutaneous alternative and can be performed on an outpatient basis under local anesthesia and with faster return to normal activities than surgery.

KEY WORDS: Varicocele - Phlebography - Varicocele, diagnosis.

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This review is based on the complete literature on the pathophysiology, the diagnosis and the treatment of varicoceles. In the topic "pathophysiology", the different hypotheses for the etiology of varicoceles are explained and discussed. Also the pathogenesis of how a varicocele could be related with infertility is described. New findings from our own studies are reported and discussed. We also try to find an answer to the questions why a varicocele is predominantly at the left side and if a varicocele is a progressive disease. Whether or not treatment is considered, clinicians need a correct diagnosis of varicoceles with strictly accepted criteria to decide which patients benefit from treatment. Besides physical examination, that remains the most used technique for varicocele diagnosis, other non-invasive techniques like color Doppler ultrasound (CDUS), thermography and scintigraphy seem to provide additional information. Venography, still considered as "the gold standard" for a varicocele diagnosis, is presently only performed when endovascular treatment is considered.

For the treatment, surgical and percuta-

2.1 Pathophysiology, diagnosis and treatment of varicoceles: a review.

Pathophysiology, diagnosis and treatment of varicoceles: a review.

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ABSTRACT

In this article we reviewed the pathophysiology, diagnosis and treatment of varicoceles.

The etiology and pathogenesis of varicoceles cannot be explained by one theory. Valve dysfunction, ontogenetic collateral formation and the nutcracker phenomenon seem to act synergistically. Hyperthermia, elevated hydrostatic pressure and antisperm agents are suggested as possible causes for the pathophysiology how varicoceles induce infertility. However the combination of patient's lifestyle, genetic factors and the consequences of reflux into the pampiniform plexus are believed to contribute to the infertility.

Although venography stays the gold standard, the combination of physical examination, color Doppler ultrasound and thermography has the highest sensitivity and specificity to diagnose a varicocele. Regarding infertility, we are still searching for strict criteria or grading, to decide which patients with a varicocele may or may not have benefit from treatment.

Treatment of varicoceles can be performed by different open, mostly surgical techniques and by percutaneous, mostly endovascular techniques. Treatment of varicoceles for infertility or to prevent infertility remains controversial, because the majority of men with varicoceles are still fertile. At the moment, inguinal or subinguinal microscopic surgery gave the highest pregnancy rates, the lowest recurrence and lowest complication rates. But retrograde superselective glue embolization or sclerosing of the ISV are the best percutaneous alternative and can be performed on an outpatient basis under local anesthesia and with faster return to normal activities than surgery.

KEYWORDS: varicocele - pathophysiology - diagnosis - treatment

INTRODUCTION:

This review is based on the complete literature on the pathophysiology, the diagnosis and the treatment of varicoceles. In the topic "pathophysiology", the different hypotheses for the etiology of varicoceles are explained and discussed. Also the pathogenesis of how a varicocele could be related with infertility is described. New findings from our own studies are reported and discussed. We also try to find an answer to the questions why a varicocele is predominantly at the

left side and if a varicocele is a progressive disease. Whether or not treatment is considered, clinicians need a correct diagnosis of varicoceles with strictly accepted criteria to decide which patients benefit from treatment. Besides physical examination, that remains the most used technique for varicocele diagnosis, other non-invasive techniques like color Doppler ultrasound (CDUS), thermography and scintigraphy seem to provide additional information. Venography, still considered as "the gold standard " for a varicocele diagnosis, is presently only performed when endovascular treatment is considered.
For the treatment, surgical and percutaneous endovascular techniques are used, both based on the interruption of retrograde reflux of blood from the internal spermatic vein (ISV) into the pampiniform plexus (PP). All techniques are explained, discussed and compared with each other, in order to find out which technique is the best treatment choice for a patient dealing with a varicocele. Up to now, there's still a lot of controversy whether a varicocele treatment is effective as an infertility treatment and as a treatment to prevent further infertility. The present criteria and recommendations are discussed.

BODY:

Pathophysiology of a varicocele

A varicocele is an abnormal enlargement of the PP. The PP is located at the posterior part of the testicle and forms the head component of the spermatic cord. Veins of the PP unite to form 3 or 4 veins before the external inguinal ring, pass through the inguinal canal and enter the abdomen through the internal inguinal ring by 2 veins. These 2 veins drain into a single ISV (Fig1). Inside the spermatic cord additional drainage of the PP occurs via the scrotal, cremasteric, deferential, and external pudendal and spermatic veins (Fig 2).

Primary varicoceles (unraveled etiology) should be distinguished from secondary varicoceles that are caused by external compression (abdominal neoplasms or inguinal canal masses). A secondary varicocele associated with unilateral right varicocele in older men is suspicious for a situs inversus and renal or retroperitoneal masses [(1)].

It is widely accepted that a dilatation of the PP develops from an inversion of the normal pressure gradient between testicle and renal vein (RV) with retrograde reflux of blood through the ISV into the PP. The higher frequency of left-side varicocele and the unique anatomy of the left ISV are the basis for several theories explaining the reflux in varicoceles on an anatomical base.

Missing or insufficiency of the ISV valves

In a physiological state, reflux in veins, particular in an upright position is controlled by the presence of functional valves. Missing or insufficient valves in the ISV allow reflux of blood. In the ISV, the existence and the number of valves have been issue of controversy. Anatomical studies on dissected internal spermatic veins demonstrated functional valves at the outflow in the RV in 32% at the left side and in all cases at the right side [(2)]. In several cadaver dissections, Ahlberg et al. discovered more valves in the ISV at the outflow zone with the RV than at the inguinal part of the ISV [(3)]. However, Sofikitis et al. found an opposite distribution of the valves in the ISV: all 49 cadavers had functional valves at the inguinal level whereas only 30 showed valves at the upper ISV [(4)]. Wishabi at al. detected no valves at all in his dissections and even confirmed his results with antegrade venography in normal and varicocele patients [(5)].
Regardless the scientific significance of the pure anatomical studies, large retrograde venography

Fig 1: Normal testicle venous drainage

The pampiniform plexus (PP) drains in the spermatic cord through the inguinal canal, from the external inguinal ring (EIR) up to the internal inguinal ring (IIR). Duplicated veins outside the inguinal canal unite to form the internal spermatic vein (ISV)

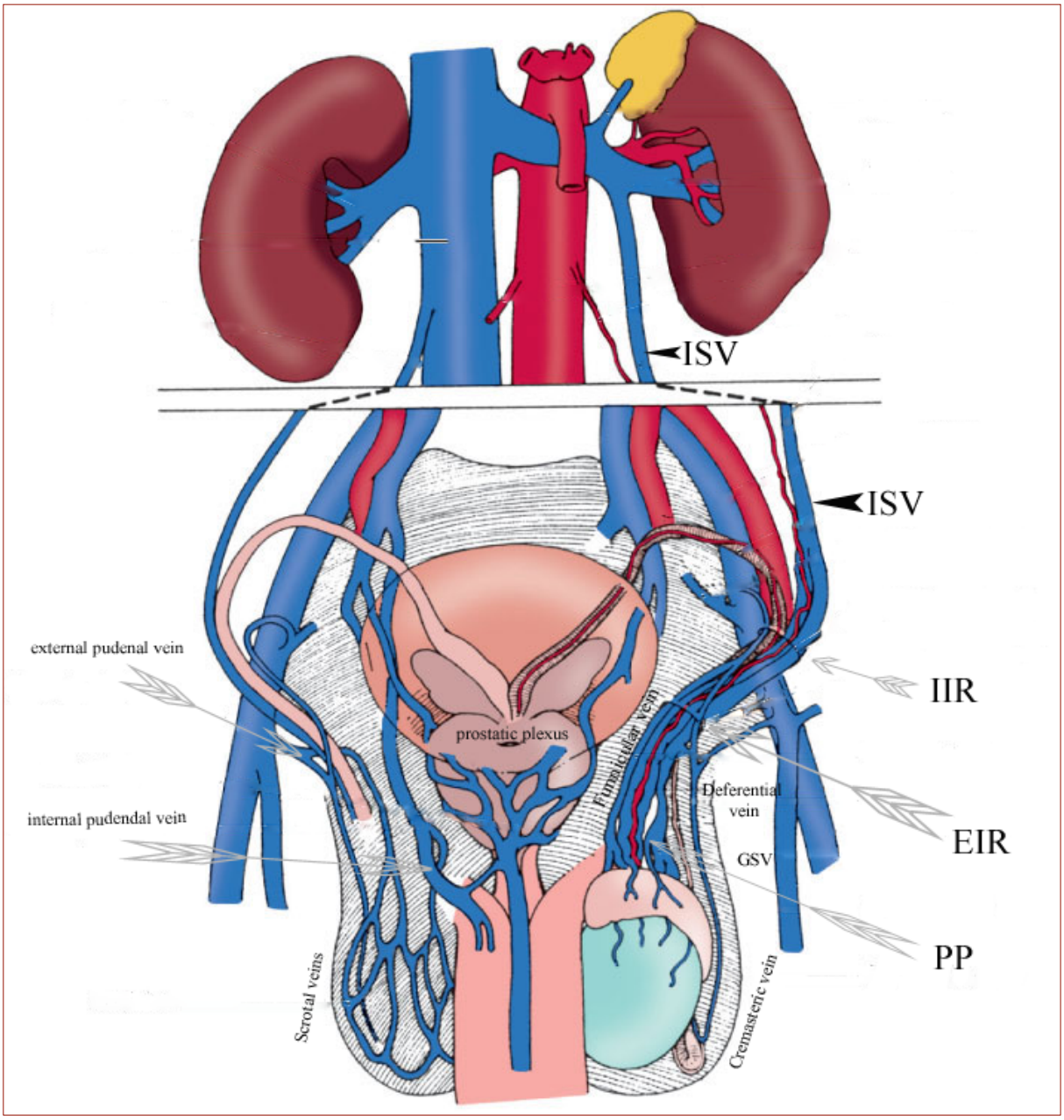
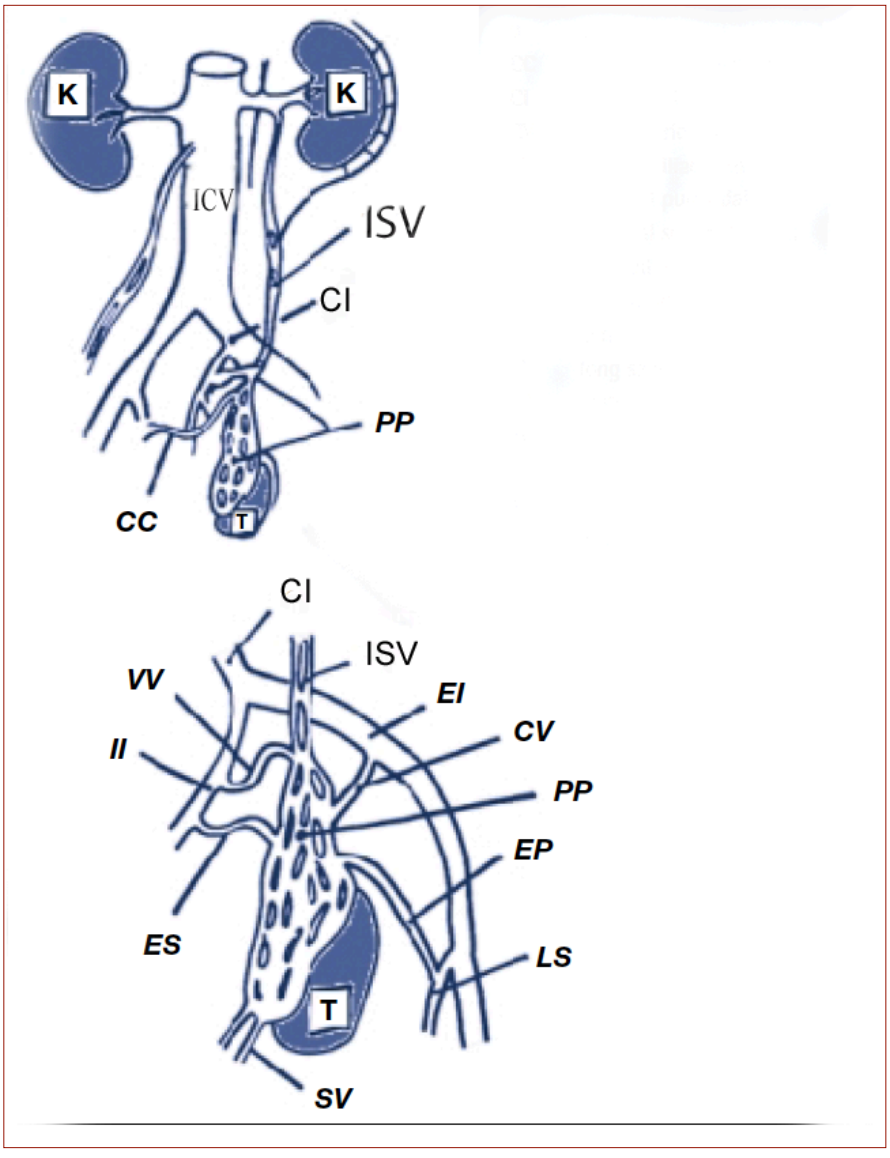


Fig 2: Anatomy of normal venous drainage of the left testicle.

CC = cross-communications, CI = common iliac vein, CV = cremasteric vein, EI = external iliac vein, EP = external pudendal vein, ES = external spermatic vein, II = internal iliac vein, ICV = inferior caval vein, K = kidney, LS = long saphenous vein, PP = pampiniform plexus, ISV = internal spermatic vein, SV= scrotal veins, T =testicle, VV = vasal vein



studies demonstrated that in 75% of left varicoceles, the outflow valve is incompetent and probably the main cause of reflux [6, 7]. These studies also demonstrated that in the presence of an insufficient outflow valve, competent valves on different levels in the ISV could block the reflux. However, the number of functional secondary valves is low. In an unpublished study, we found at least one secondary valve in the ISV in N=52/218 (23%) and in N=12/80 (15%) adults and in N=18/191 (9%) and N=3/28 (10.7%) adolescents respectively at the left and at the right side. If missing or insufficient valves were the main cause of reflux, would we not expect varicocele to be a bilateral disease? In the aforementioned study, we found that only 28.3% of varicocele patients had an insufficiency of the right ISV with a significant difference between adults (39.6%) and adolescents (15.6%). In both groups, the right varicocele was attributed to outflow valve dysfunction in only 15-17.8%. We did not find arguments for a distinct valve disease affecting both the left and the right outflow valve in the same patient. Is the valve insufficiency a primary disease or the secondary result of chronic reflux, elevated pressure and venous dilatation? We did not find a difference in diameter of the ISV between adults and adolescents, at least not in the left varicocele. In the right-sided varicocele however, the diameter was significantly larger in adults, but the number of dysfunctioning valves not. Thus, although the question is still unraveled, there are little arguments for a secondary valve dysfunction. Despite the presence of competent outflow or secondary valves, contrast reflux into the PP could be proved in all our cases as in the previously mentioned studies.

Ontogenetic differences

Braedel et al proposed an ontogenetic etiology for the development of an idiopathic left varicocele that rejects the theories of missing valves [7]. The embryological development of the left ISV from the subcardinal veins is a complex process where all veins (ISV, adrenal veins and RV) have to converge into the single left RV (in contrast to the right side where the veins drain directly in the caval vein). Braedel argued that a poorer drainage ensued from these involuting veins. These veins remain open during embryogenesis to form a collateral draining network, which would correspond with the medial and lateral collaterals we observed on phlebograms and, again according to Braedel, would be the major cause of varicoceles. The variable expression of varicoceles in adulthood is according Braedel directly associated with the variability in timing and extent of the venous system involution. He claimed that his theory is consistent with the predominant unilaterally and the high frequency and occurrence of left varicocele even in childhood. Indeed, previous reports and our unpublished study proved the high incidence of such collaterals (N=262/409, 64%)[8]. However, we have found a significant different number of collaterals between adults and adolescents at the left side (70.6% versus 56.5%, P=0.03). If ontogenesis should be the main cause of varicoceles, would we not expect as much collaterals in adolescents as in adults? It seems that besides an ontogenetic cause other mechanisms play a role as well.

Fig 3: Nutcracker phenomenon in a varicocele confirmed on Computed Tomography (CT).

Left: Axial contrast enhanced CT in a patient with compression of the renal vein (small arrow) as it courses between the superior mesenteric artery (upper arrowhead) and abdominal aorta (lower arrowhead). This has caused left renal vein outflow obstruction and dilatation of the ISV (big arrow) with formation of numerous perirenal venous collaterals (star).

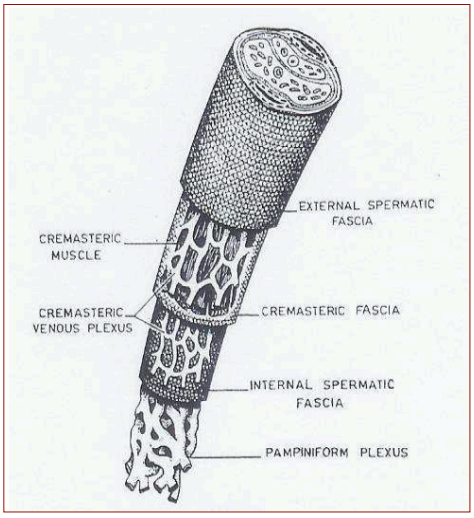
Right: Dilated left ISV on axial CT (arrow). As with the perirenal collaterals (star), venous outflow obstruction has led to alternative venous drainage routes for the left kidney to decompress the renal venous hypertension.

Table 1: Nutcracker types according to Coolsaet. *(Coolsaet et al.. The varicocele syndrome: venography determining the optimal level for surgical management. J Urol. 1980.)*

Types	Features
1	Proximal high nutcracker caused by compression of the left renal vein between the aorta and the superior mesenteric artery
2	Distal low nutcracker: caused by compression of the left common iliac vein by the left common iliac artery
3	A combination of types 1 and 2

Fig 4: Fasciomuscular tube of the ISV according Shafik et al. *(courtesy by Shafik. The fasciomuscular tube of the spermatic cord. A study of its surgical anatomy and relation to varicocele. A new concept for the pathogenesis of varicocele. Fertil Steril 2011. Br J Urol 1972.)*

The fasciomuscular tube consists of three layers, the external and internal spermatic fasciae, and in-between the cremaster muscle with his fascia. These layers are extensions of the anterior abdominal wall musculature.



Nutcracker phenomenon

A third theory emphasized a compression of the left RV between the aorta and superior mesenteric artery, known as the “nutcracker phenomenon” [9] (Fig 3). This compression increases the hydrostatic pressure in the ISV, causes reflux by decrease of the pressure gradient between the RV and the PP and finally induces the dilatation of the PP. Later on, Coolsaet proposed 3 nutcracker subtypes in varicoceles (Table 1) [10]. A proximal, type 1 or high nutcracker type caused compression of the left RV by the aorta and the superior mesenteric artery. A distal, type 2 or low nutcracker type caused compression of the left common iliac vein by the left common iliac artery. Type 2 leads to reflux into the deferential and cremasteric veins. Type 3 is a combination of types 1 and 2 and may also be accompanied by venous hypertension and retrograde flow. Coolsaet also suggested a complementary occlusion of the deferential vein in type 2 and 3.
Sayfan et al. demonstrated in 1984 with antegrade venography, cadaver dissections and laparoscopy, the compression of the superior mesenteric artery on the RV in some varicocele patients [11]. Lau et al described in 1986 a case of a retro aortic left RV compression as "a posterior nutcracker" which induced RV hypertension [12]. Although venography and CDUS criteria and characteristics were described and associated with a " nutcracker ", a high left RV to inferior caval vein (ICV) pressure gradient is the gold standard for diagnosis [13]. Patients with varicoceles could have such a pressure gradient, but it is not a consistent feature in all varicocele patients [14]. Pressure gradients in varicocele patients were detected in supine and semi-erect position but did not increase in erect positions [15] [16]. The importance of a nutcracker in the pathogenesis of varicoceles is controversial.

Spermatic cord disturbances

An older but intriguing theory suggested that a disturbed pump mechanism of the fasciomuscular tube around the spermatic cord and defects in the wall of the spermatic cord might induce varicoceles. Shafik demonstrated that varicocele patients had atrophy of the collagen of the fasciomuscular tube, which makes the tube less resistant, resulting in venous dilatation and stasis (Fig 4) [17]. He suggested that simultaneous contraction of the fasciomuscular tube by the cremasteric muscle in association with the elasticity of the internal and external spermatic fasciae prevents reflux from the abdominal part of the ISV [18]. In non-varicocele patients, the elevation of intra abdominal pressure tightens the tube around the spermatic cord. In association with closure of the valves in the PP, reflux from the abdominal part of the ISV is prevented.
In 1985 Sayfan et al refuted the theory. After indirect inguinal hernia surgery with routine dissection of the tuba, there were no postoperative varicoceles. His suspicion was confirmed by a prospective study [19].
Non-anatomical hypotheses for dilatation of the PP are not based on the reflux of venous blood but on the increased arterial supply or on local dilating agents.

Increased arterial blood during puberty

This hypothesis is based on the higher incidence of varicoceles during puberty. Akbay et al. investigated 4052 boys (2-19 years) and demonstrated a significant increase of varicoceles prevalence [20]. During puberty, increased arterial blood flow to the testis should exceed venous capacity at the PP, resulting in venous dilatation and varicocele. This theory is not confirmed in humans. Animal experiments are conflicting [21]. However the increased arterial blood flow theory

is unrealistic as the capillary network serves as a pressure reducer. The direct effect of the dilatation of the venous drainage system is only possible in arteriovenous anomalies.

Elevated nitric oxide

Nitric oxide is a potential vasodilator. Ozbek et al. published a significant elevation of nitric oxide in the veins of the PP in contrast to peripheral veins [22].

Is a varicocele a progressive disease?

Akbay et al reported a clinical varicocele prevalence of 7.2% in 4052 boys. In 1232 children aged 2 ± 10 years, varicoceles were present in 0.92%. In 2531 adolescents aged 11 ± 19 years, 11.0% had a varicocele, which is a significant difference ($P<0.001$). He detected a significant prevalence increase at the age of 13 years ($P<0.005$) with an increasing testicular atrophy with puberty and concluded that varicocele is a progressive disease [20].
In our unpublished study, we compared phlebographic characteristics of varicoceles between adults and adolescents. The incidence of valve dysfunction, renospermatic bypasses and the nutcracker phenomenon was higher in adolescents than in adults. These findings are disconcordant with a purely evolutionary disease of the left-sided varicocele. On the right side however, the phlebographic diameter of the ISV, the number of medial collaterals and the incidence increase with age, which could support the theory of a progressive disease.

Is a varicocele a predominantly left-sided disease?

Akbay detected only 10.8 % bilateral varicoceles in 279 boys by physical examination [20]. Most articles based on venography and with large number of patients report a bilateral varicocele in 25% [23-25]. In studies using different diagnostic tools, bilateral varicocele was reported to range between 40 % and 60% [26, 27]. Mali et al. contested such high percentages of a right-sided varicocele, ascribing it to a misinterpretation of the phlebograms. Mali et al. proved with radionucleotide studies that reflux to the PP is not real when contrast injection through the outflow valve is performed under wedge conditions [28]. Gat et al. questioned the fact that varicocele should be considered as a mainly left-sided disease. In reports on adolescents and infertile males, they detected a bilateral varicocele in more than 80% with venography [1].

Pathophysiology of the association of varicocele with testicle hypotrophy and infertility

Clinically detectable varicoceles can be associated with an impaired spermatogenesis (abnormal sperm count, motility, morphology, gonadotropin level and histological changes) with testicle hypotrophy and infertility [29]. Mac Leod reported as the first, the “stress pattern” in varicocele patients in whom the sperm is elongated with tapered head and amorphous cells [30]. Human and experimental animal studies showed a lower number of morphologically normal sperm in varicoceles [31]. However, some infertile men with a clinical varicocele have normal sperm count and morphology. Many causes are suggested to explain the association between varicoceles, sperm abnormalities, testicle hypotrophy and infertility, and hence the pathophysiology of infertility.

Hyperthermia

Increased temperature at the testicle can be caused by increased venous reflux of warm blood from the core of the body or by a disturbance of the countercurrent heat exchange system.

The backflow of warmer renal venous blood was first described by Tessler et al. and is based on reflux [32].

The heat exchange hypothesis postulates that in the spermatic cord, the draining blood from the PP cools off the entering arterial blood [33]. The PP controls the temperature around the testicle by an efficient drainage of the testicle venous blood into the ISV. This mechanism keeps the temperature 1-2°C lower at the scrotum than at the core body. Impairment of this countercurrent mechanism, by for instance dilation of the PP, produces an elevation of the testicular temperature. Saypol et al. investigated intra-testicular temperature changes caused by a varicocele and showed a bilateral increase after partial occlusion of the RV or ligation of the ISV in animals [34]. Experimental cryptorchidism mimics a more chronic state of testicular hyperthermia comparing to venous ligation. In adult volunteers, wearing an athletic supporter during the day to hold the testes in the inguinal canal caused a higher testicular temperature and a diminished sperm quality. The latter returned to normal within 12 months after omitting the supporter [35]. Other investigators found similar histological changes in testicular tissue from biopsies of men with varicocele and cryptorchidism [36]. Induced cryptorchidism or testicular heating in animal experiments as well as data from human recreational wet heat exposure (hot tubs, Jacuzzis, or hot baths), showed a deteriorating effect on sperm parameters [37]. However, there are reports on abnormal scrotal temperature in men with and without varicoceles [38]. Other data showed no difference in scrotal temperature between infertile men with and without a varicocele [39]. The critics on all these studies were that the scrotal temperature varies widely with body position and activity during the day.

How hyperthermia affects spermatogenesis remains unraveled. Elevated testicular temperature should cause damage to the DNA and proteins in the nucleus of the seminiferous tubule cells and/or Leydig cells [29]. Testicular hypotrophy (between 10 and 20%) is directly related with loss of seminiferous tubules and germinal cells, which make up 98% of the testis. Heat may increase germ cell apoptosis, affect androgen production and as a consequence sperm production [38]. It is not relevant in this review to discuss in detail the pathways of hormonal dysfunction in varicoceles.
Hyperthermia could also be induced by increased arterial inflow during puberty, overwhelming the countercurrent thermal exchange system [34].

Elevated venous pressure

This theory is based on an increased venous pressure in the ISV and the PP, which could not only limit arterial inflow on testicle level but also interfere with the osmotic regulation of metabolic products. Accumulation of toxins might exert a detrimental effect on the testicle epithelium [40]. Impairment of the vascular drainage with venous stasis was proved by scintigraphy and retrograde venography [28] [41]. The abnormal counter pressure would cause chronic vasoconstriction of the testicular arterioles, which may lead to persistent hypoperfusion, stasis and hypoxia [42]. The hypoxia would lead to the accumulation of different gonadotoxines like reactive oxygen species [43].
Pressure measurements in varicocele patients were performed antegrade by direct puncture of the PP. Sayfan et al. punctured the ISV and registered a mean pressure of 18.73 mm Hg in 45° semi-

erect position at the inguinal ISV [44]. As these authors found similar pressures in a non-varicocele control group, they saw no association between increased venous pressure and subfertility in varicoceles. Other investigators detected that the pressure was 20 mm Hg higher in the varicocele group than in the control group [45]. However, the absolute pressures retrievable from both studies of Shafik and Bedeir were inconceivably high with pressures of 80 mm Hg or more [45] [46]. A mean hydrostatic pressure of 60 mm Hg in 30 normal ISV's is unrealistic and probably caused by a methodological error.

In an unpublished study, we performed direct pressure measurements in the inguinal ISV in 45° semi-erect position. We found a pressure of 33 mm Hg that is composed of a hydrostatic pressure (at least 20 mm Hg) and a systemic venous pressure (12 mm Hg). This absolute intravenous pressure seems high enough to act as a counter pressure that could impair arterial supply and hence spermatogenesis.

Adrenal venous reflux

Mac Leod suggested that high concentrations of adrenal cortical hormones might be a possible cause of damage of the seminiferous epithelium [30]. Metabolic products from the renal or adrenal venous circulation may accumulate in the PP during chronic venous reflux from the RV into the ISV. Several authors did not find these higher concentrations in the ISV blood [47, 48]. Comhaire and Vermeulen detected higher concentration of catecholamines [47]. Reflux of catecholamines rich blood, could result in vasoconstriction (by the noradrenaline) of the intratesticular arterioles and contribute to testicular hypoxia. Injection of labeled microspheres or adrenalectomy in animal experiments did not confirm the hypothesis of reflux of adrenal metabolites as a cause for infertility in varicoceles [49] [42].

Toxic agents

Identical levels of toxic agents are found in varicocele patients as well as in a non-varicocele control group, which were exposed to the toxic agent. Human and animal studies proved that cadmium or cigarette exposure affects spermatogenesis and has a negative impact on sperm parameters [40, 50]. Animal feeding with cadmium led to decreased sperm count and motility, germ cell apoptosis and finally Leydig cell dysfunction [50]. An intriguing observation is that seminal cadmium levels in varicocele patients are elevated, similar to cadmium levels in cigarette smokers and cadmium workers [51].

Autoimmunity (antisperm-antibody formation)

This theory suggests that varicoceles cause a disruption of the normal blood-testis barrier with the production of antisperm antibodies. These antisperm antibodies induce macrophage reaction with phagocytosis and immobilization of the spermatozoa. This results in an impairment of sperm penetration into the cervical mucus (dysfunction of the acrosome reaction) [38,52]. Animal experiments with artificially induced varicoceles are conflicting regarding the increased antibody levels [53] [54]. In a human study, direct immunobead assays detected no alteration of the autoantibody level in infertile men with varicoceles [55]. The available data suggest that infertile men have higher concentrations of antisperm antibodies than fertile men and that infertile varicocele patients have similar percentages as infertile males without varicoceles. The theory of antisperm antibodies requires further evidence-based studies.

Acrosome reaction

This reaction is a fusion of the membrane of the acrosome of the sperm's head with the zona pellucida of the plasma membrane of the oocyte. After the fusion, the contents of the acrosome (like surface antigens and enzymes) allow fertilization to occur.
Varicoceles should induce a defect of the acrosome reaction.
The theory was postulated after observation of varicoceles in unexplained normospermic (idiopathic) male infertility. Rather a failure of sperm function than a defect of morphology or an insufficient quantity of sperm would be the etiology of subfertility.
No animal experimental studies have been published to confirm this theory. Up to a 45% abnormal acrosome reaction is found in infertile men with a varicocele, which normalized after varicocelectomy [(56)].

Oxidative stress

The hypothesis is based on an excess production of reactive oxygen species (ROS), while a balance in concentration is necessary for normal sperm function. Too high concentrations of ROS oxidize fatty acids in spermatozoa membranes and cause DNA damage with fragmentation of the sperm [(57)]. Studies have shown that infertile men with varicoceles have higher levels of seminal oxidative stress markers (ROS, lipid peroxidation) than fertile men and infertile men without varicoceles [(58)] [(59)].
Agarwal et al. reported a meta-analysis based on 23 human studies that confirmed that oxidative stress is likely to play a role in the etiology of varicocele-related infertility [(60)]. While many studies show that seminal ROS levels are higher in varicoceles than in controls, others have questioned the association between varicoceles and ROS levels [(61)].

The importance of ROS in the varicoceles pathophysiology is supported by studies that could improve semen parameters in men with varicoceles after oral administration of antioxidants (i.e. glutathione, carnitine) [(62)]. After varicocelectomy, oxidative stress biomarkers decrease and antioxidant capacity increases, which suggests that oxidative stress in the seminal fluid is primarily caused by the varicocele itself [(58)] [(59)]. A lot of non-randomized prospective and retrospective studies have demonstrated that varicocele repair is associated with reduced sperm DNA damage [(63)].

In summery, the pathogenesis of varicoceles is apparently not explained by one mechanism or theory. Several hypotheses seem to act synergistically. Valve dysfunction and ontogenetic collateral formation both seem important in the pathogenesis of varicoceles, the first probably in adolescents and the latter in adults. The nutcracker-varicocele association seems an additional etiology of varicoceles that is more relevant in adolescents.

Concerning the relation varicocele-infertility, hyperthermia is constantly related with varicoceles. Elevated hydrostatic pressure in the PP could point at an imbalance at the capillary-venous level, hence impairing arterial supply. However, we lack data on venous pressures in non-varicocele patients. Until physiological studies are completed, the role of hydrostatic pressure elevation cannot be fully determined.

Anti sperm agents are more often found in infertile male with varicoceles than in fertile male, and normalize after varicocele therapy. These agents are probably primary causes of the infertility since they are also found in non-varicocele infertile men. Elevated scrotal temperature resulting in

oxidative stress with the formation of ROS is a theory that gains more support to explain the detrimental effects of varicoceles on testicular function [38].

Table 2: **The Dubin classification**. *(Dubin and Amelar. Varicocele size and results of varicocelectomy in selected subfertile men with varicocele. Fertil Steril 1970.)*

Grade	Features
1	Small scrotal varicose veins are only palpable after the Valsalva maneuver
2	Dilated veins are moderate in size and palpable without the Valsalva maneuver
3	Large varicose veins like "a bag of worms" are visible through the scrotal skin without Valsalva

Table 3: **Grades of reflux according Cornud**. *(Cornud et al.. Varicocele: strategies in diagnosis and treatment. Eur Radiol 1999)*

Grade	Features
Brief	Physiological reflux takes less than 1 second
Intermediate	Reflux is obvious during 1or 2 seconds and decreases during the Valsalva maneuver and finally disappears before the end of the maneuver
Permanent	Continuous reflux that takes more than 2 seconds and showed saturation during the Valsalva maneuver

Table 4: Simplified color Doppler ultrasound classification of varicoceles according Pauroso. *(Pauroso et al. Varicocele: Ultrasonographic assessment in daily clinical practice. J Ultrasound 2011)*

Grade	Features
1	Reflux in the vessels of the inguinal canal that is observed only during the Valsalva maneuver and absence of varicosity on standard ultrasonography
2	Small varicosities with reflux seen only during the Valsalva maneuver
3	Enlarged vessels which caliber increases during the Valsalva maneuver
4	Obvious vessel enlargement with reflux that is present under basal conditions and does not increase during the Valsalva maneuver

Fig 5: A visible varicocele in rest looks like a bag of worms: Grade 3 according Dubin and Amelar
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Fig 6: Sagittal gray scale 2D-ultrasound of a hypotrophic left testicle with an underlying varicocele (white arrow).

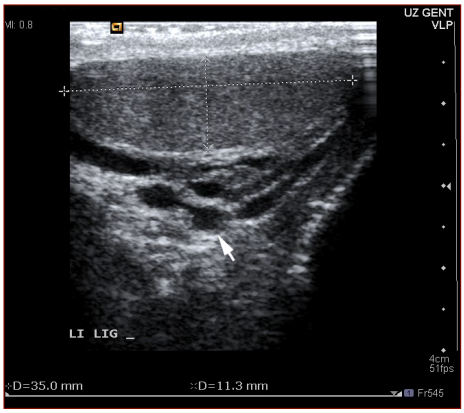


Fig 7: Sagittal CDUS at the ISV and the PP during normal breathing and after Valsalva maneuver.

Upper left: An-echoic tortuous tubular structure of enlarged veins (diameter 2.8 mm) with no spontaneous flow or reflux (arrow) during normal breathing. Normal color flow in the testicular artery (arrowhead).

Upper right: Increase of the diameter to 4.5 mm and detection of continuous reflux during more than 2 seconds after Valsalva maneuver.
Lower left: Dilated ISV (diameter 2.6 mm) with spontaneous flow during normal breathing (arrow).
Lower right: Increase of the diameter to 3.3 mm and detection of continuous reflux during more than 2 sec. after Valsalva maneuver (arrow).

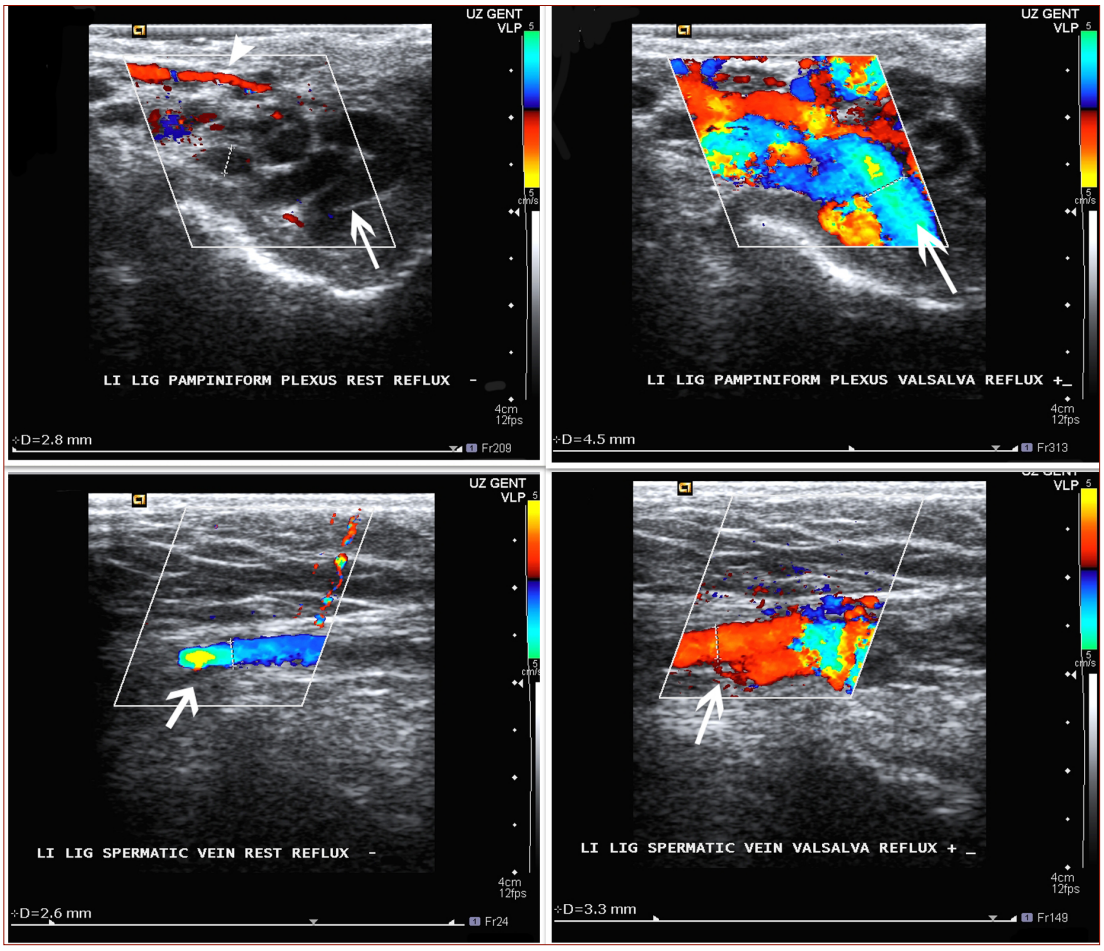


Fig 8: Shunt and stop-type varicocele *(courtesy by Mohseni. Shunt-type vs. stop-type varicocele. Fertil Steril 2011.)*
(A) Anatomy of the shunt-type varicocele, which shows incompetent valves and shunting from the ISV through the communicating veins, which results in continuous reflux of blood (retrograde and antegrade) into the PP and increase of the venous diameter.
(B) Anatomy of the stop-type varicocele, where the reflux in the ISV is stopped by a competent valve above the level of the communicating veins, which results in a brief reflux only and a slightly increase of the venous diameter.

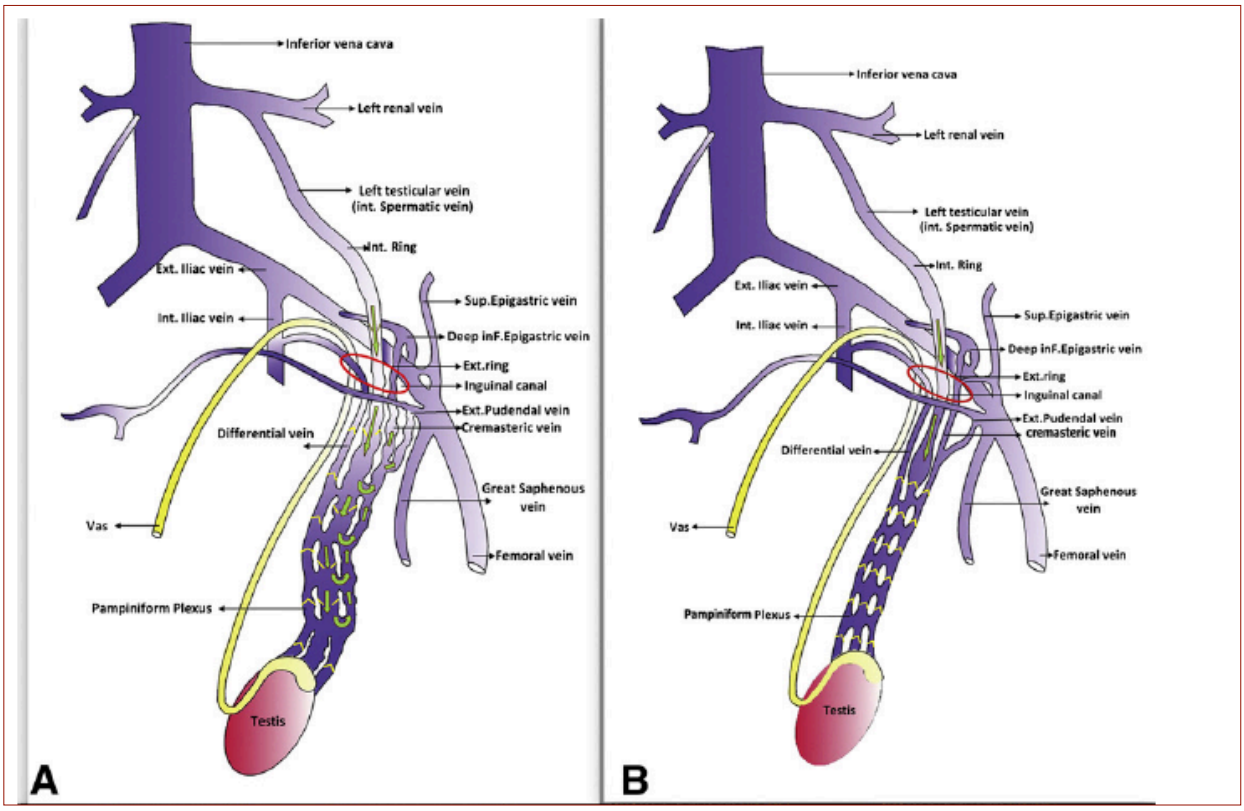
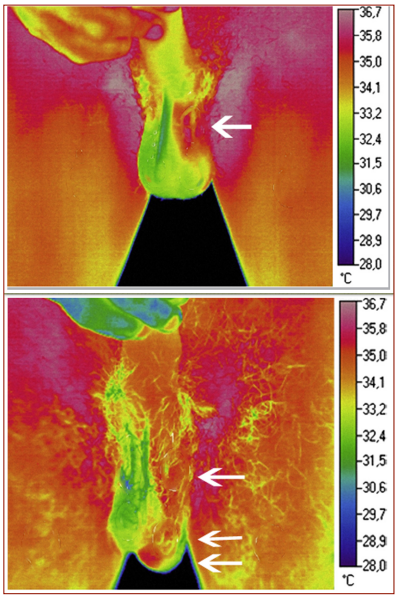


Fig 9: Digital scrotal thermography

Upper: Digital thermography with elevation of the temperature only at the PP (arrow).
Lower: Digital thermography with elevation of the temperature at the PP (arrow) and at the testicle (arrows).



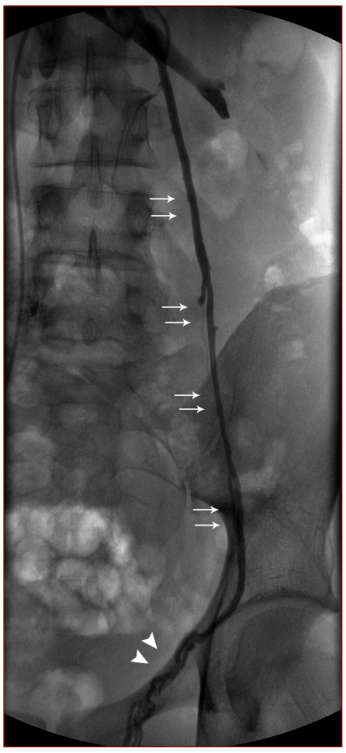
Diagnosis

Clinical varicoceles can be detected by physical examination whereas subclinical varicoceles can be only diagnosed by imaging, such as color Doppler ultrasound (CDUS), thermography, scintigraphy or venography.

Physical examination of the scrotum remains the most commonly used technique to diagnose varicoceles. Palpation of the scrotum is best performed in a relaxed patient in standing position, in a warm room and carried out by a well-trained physician.
The severity of a clinical varicocele can be expressed by the Dubin system classification (Fig 5)(Table2) [64]. However, physical examination has sensitivity between 50% and 70%, which is rather low [65] [66]. The technique is not reliable in men with small varicocele, or in abnormal scrotal anatomy (e.g., a concomitant hydrocele, previous scrotal surgery, morbid obesity, lipoma of the cord or scrotal wall thickness). In right-sided varicoceles, palpation alone is inadequate, missing almost 90% of the varicoceles [67].

Therefore in clinical and subclinical varicoceles additional imaging tools are nowadays mandatory. CDUS has become the most widely accepted modality.
With 2-D real-time ultrasound the size of the testicles can be measured and compared very quickly and the location, size and the bilateral presence of the varicocele determined. Testicular size reduction of more than 20% or 2 ml is highly suspect for an underlying varicocele (Fig 6). The varicocele appears as an an-echoic tortuous tubular structure of enlarged veins, which increases in diameter during Valsalva maneuver. However, there is no generally accepted minimum diameter above which the vein becomes a varix [68]. A dynamic CDUS seems more reliable because it detects reflux in the dilated veins (Fig 7). Reflux lasting for more than 1 second (spontaneously or after Valsalva maneuver) has sensitivity and specificity of 97% and 94% respectively to detect phlebographically confirmed varicoceles [66, 69]. Others propose a permanent reflux for more than 2 seconds to increase the sensitivity to almost 100%, but at cost of a lower specificity (Table 3) [70]. A number of varicoceles (probably subclinical) will be missed with a threshold of 2 seconds. CDUS results have been classified to guide management of varicocele by studying the fluxes in the inguinal ISV and the PP by changing patient's position from supine to upright, with and without Valsalva maneuver. However the 5 grades Sartechi classification or the simplified Pauroso (Table 4) did not fulfill such expectations [71, 72]. Up to now, there is no consensus concerning the grading of CDUS and the indication for varicocele treatment. Despite improvements of sperm parameters, an increase of pregnancy rates and a disappearance of the varicocele on physical examination, Cvianic et al. detected in 64% color flow in veins more than 2 mm after varicocelectomy [73]. They contributed the anatomy of a shunt-type varicocele for the persistence of antegrade and retrograde flow in the PP. Sigmund et al. introduced an intriguing concept of stop-type and shunt-type varicocele (Fig 8) [74]. In the stop-type, only the ISV is dilated and reflux is stopped before the level of the communicating veins by a competent valve. Therefore the stop-type should demonstrate at CDUS, hardly reflux and slightly dilation of the veins in the PP after Valsalva maneuver. In the shunt-type however, a kind of venous bypass from internal to external spermatic (cremasteric) veins exists which causes both antegrade and retrograde flow and dilation of both venous systems.

Fig 10: ISV venography
RV venography under Valsalva maneuver with reflux through the ISV (double arrows) into the PP (double arrowheads).



CDUS shows then a continuous reflux and a clear diameter increase of the PP after Valsalva maneuver. CDUS is non invasive and doesn't involve ionizing radiation. If performed adequately, CDUS imaging has the potential to be the gold standard for the diagnosis of varicoceles. However, we should keep in mind that reversal of flow less than 2 sec can also be observed in healthy fertile males without a varicocele and after varicocelectomy [73, 75]. Both clinical and CDUS data are important to diagnose a varicocele and to exclude a recurrence.

Thermography measures the temperature on the scrotal skin surface. Renal venous blood that refluxes into the ISV is warmer than effluent blood in the PP [32]. Kormano et al. started to use an infrared camera to detect temperature differences over the scrotal skin [76]. Patients should stand with stretched legs, the tip of the penis held against the abdominal wall and the scrotum isolated freely. After acclimatization for 10 minutes in a room of 22-23°C., the thermographic camera is placed in front of the patient on a distance of around 40 cm. Anterior and oblique images are taken in basal condition, during and shortly after the Valsalva maneuver (Fig 9). The infrared camera is a reliable diagnostic test with a sensitivity of 84-98% and a specificity of 81-100% [65] [77]. Infrared camera thermography is a simple and easy performed external application that is excellent for varicocele screening. Normal thermograms with reflux on venography were very rare, but inflammatory disease of the epididymis can be responsible for scrotal hyperthermia without venous reflux on venography [78].
Alternatively, a disposable contact strip for thermography based on liquid crystals (Varicoscreen) has been developed and tested with contradictory results [67, 69]. The Varicoscreen is no longer commercially available.

Whether quantification of digital thermography can optimize patient selection for varicocele treatment or will be able to predict the outcome of therapy is an interesting issue [79].

Venography of the ISV is considered to be the gold standard for varicocele diagnosis. In contrast to physical examination and CDUS, venography is less dependent on technical variation and inter-observer variability. Venography and superselective coaxial catheterization of the internal spermatic vein are primarily employed only when endovascular percutaneous treatment is intended. The procedure can be performed under local anesthesia by a percutaneous retrograde catheterization or antegrade cannulation after exploring the vein in the spermatic cord. Retrograde catheterization is possible by an upper (brachial or internal jugular vein) or lower (femoral vein) approach. The upper approach is less comfortable for the patient, but the ISV can be catheterized very proximally with a diagnostic catheter.

Selective venographies of the renal veins and the internal spermatic veins have to be performed. The phlebography is done in anti-Trendelenburg position on a tilt table under Valsalva maneuver with the injection of contrast-agent. Venous insufficiency is substantiated by retrograde opacification of the spermatic vein and of the PP, either spontaneously or after passing competent valves(Fig10)
But even the gold standard also has its limitations, which lead to false-positive (wedge injection under a competent valve) and false-negative results (e.g. competent outflow valves, renospermatic bypasses) [80] [28].

Fig 11: Scrotal scintigraphy of a normal patient versus a varicocele patient. *(courtesy by Mali. Hemodynamics of the varicocele. Part I. Correlation among the clinical, phlebographic and scintigraphic findings. J Urol 1986.)*
Left: 5-minute exposure without visible activity in the scrotum (black arrow).
Middle and right: 5-minute exposure and diagram show abnormal activity in the scrotum (black arrow) in a patient with a varicocele.

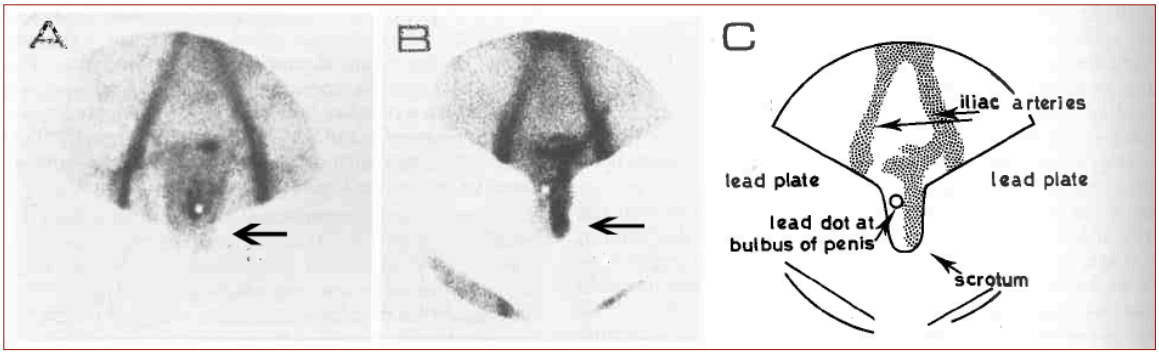


Table 5: Grades of Time activity curves

Types	Features of Time-activity curves (TAC)
1	Radioactivity shows faster accumulation and maintenance of a higher level on the left side than on the right side
2	Time-activity curve rises gradually to a higher level on the left than on the right
3	Time-activity curve increases symmetrically and slowly on both sides

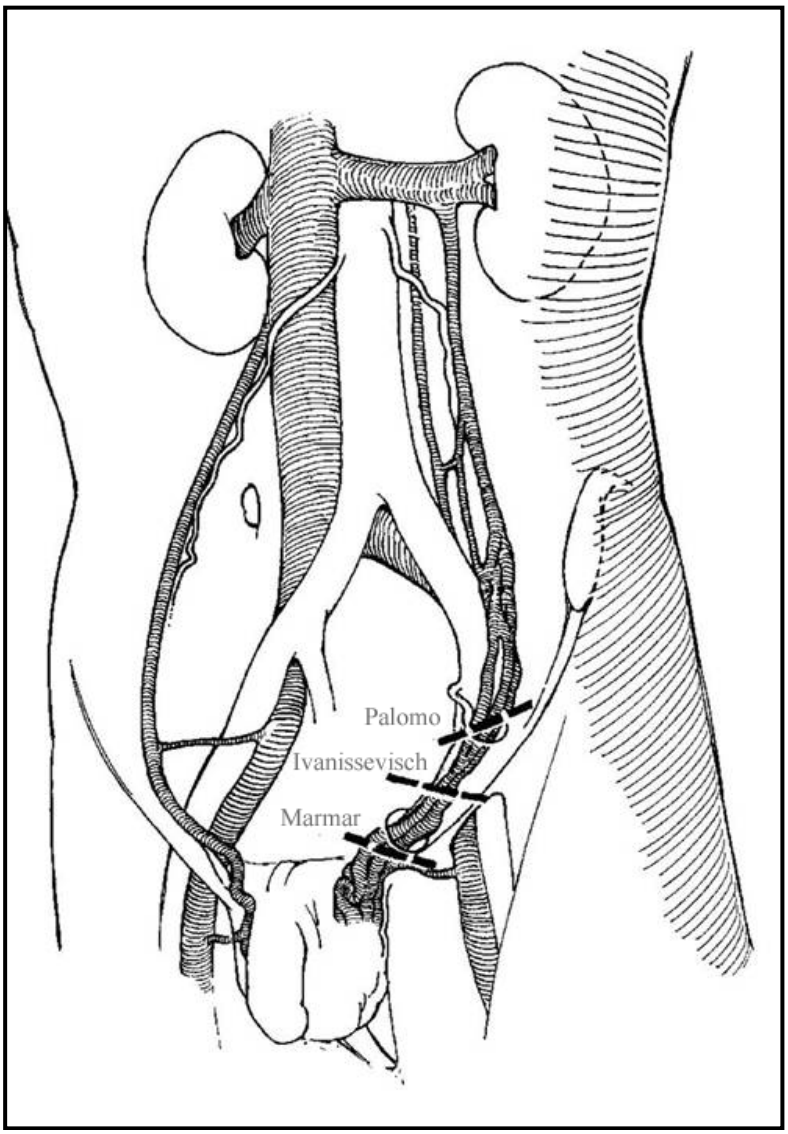
Disadvantages are the invasiveness, the radiation burden, the need for contrast material and its time-consuming aspect.
Antegrade venography is performed through a scrotal incision or under ultrasound guidance. A dilated branch of the PP is accessed using a micropuncture needle, followed by Seldinger technique cannulation of the vein. Contrast agent injections by hand demonstrate the varicocele, all testicular veins, collaterals and finally the entire length of the ISV. Routine use of intraoperative venography would help to detect missed venous vessels after initial venous ligation and would decrease reoccurrences [81]. In case of an unexplained recurrence of a varicocele, Gendel et al. demonstrated that only with antegrade PP venography anastomoses from the ipsilateral saphenous and femoral veins to the PP could be discovered [82]. However, other reports minimalize the importance of intraoperative venography in prevention of persistent varicocele [83] [84].

Contrast-enhanced multidetector CT or MR-venography could avoid the invasiveness of catheter venography with 3D imaging. Coronal maximum intensity projections (MIP) or steady state imaging with blood pool contrast agents have significantly improved the quality of the imaging of the venous system [85]. However no large series prove their use in varicocele diagnosis.
In scintigraphy, patient's red blood cells are in-vivo labeled by injecting 15 mg of stannous ions in the form of pyrophosphate 20 mCi before the intravenous administration of 99m Tc pertechnate. Scintigraphic evaluation is performed with the patient in the upright position, the penis taped to the midline of the anterior abdominal wall and the scrotum located in the lower third of the field of view. A small field-of-view gamma camera observes intra-scrotal accumulation of the radioactive tracer technetium-99-labeled red cells (Fig 11). Scintigraphy has a sensitivity of 96.5 % and a specificity of 97.1 % to diagnose a varicocele [86]. Scintigraphy provides Blood-Pool and Blood Flow images that could be divided in different grades [87]. In Blood-Pool Scintigraphy, the labeled cells accumulate in the varicocele and can be visualized as a static volume, like in 2D-ultrasound or thermography. Blood Flow Scintigraphy demonstrates the degree of venous reflux in the ISV, comparable with the reflux on CDUS [88]. Moreover, Blood Flow scintigraphy may distinguish a varicocele caused by ISV reflux from one caused by obstruction of the iliac vessels. Time-activity curves (TAC) generated from scrotal perfusion images were defined in three perfusion patterns (Table 5). Ortapamuk et al. discovered that TAC-2 and TAC-3 patients had better seminal improvement after therapy of the varicocele [89]. Although scintigraphy is a valid, non-invasive technique to objectively document and grade the severity of clinically diagnosed or suspected varicoceles, the technique is nowadays rarely applied in practice because it is more expensive and time consuming compared to CDUS.
Pathological semen analysis with oligozoospermia or asthenozoospermia could be a hint of an underlying varicocele. Elevated follicle stimulating hormone (FSH) and low testosterone are typical signs of testicular dysfunction due to a varicocele.

Because of the low sensitivity and specificity of physical examination for the diagnosis of varicoceles and even more, for the detection of subclinical varicoceles, we need additional imaging. Thermography is very sensitive and can locate the varicocele. CDUS and scintigraphy give us additional information about the size of the varicocele and reflux of blood. Venography remains the gold standard, but is only performed when percutaneous embolization is considered. CDUS, which is widely and well tolerated, seems the most practical and most accurate non-invasive tool to diagnose a varicocele. Reflux of at least 1 sec. at the dilated veins in the PP or through the inguinal ISV, in rest or under Valsalva maneuver, gives a high sensitivity for

varicocele diagnosis. The combination of CDUS and thermography has the highest sensitivity and specificity to diagnose a varicocele. Regarding infertility, we are still searching for strict criteria or a grading scale, to decide which patients with a varicocele may or may not have benefit from treatment.

Fig 12: Surgical incision sites for retroperitoneal (Palomo), inguinal (Ivanissevich), and sub-inguinal (Marmar) approaches.



Treatment

The goal of varicocele treatment is to eliminate the dilatation of the PP and hence the clinical or subclinical varicocele. Both the surgical and endovascular treatment options are based on the interruption of retrograde flow into the PP from the ISV or from collateral veins.

Surgery

The surgical approaches can be classified in techniques ligating the ISV above or below the internal inguinal ring. A varicocelectomy can currently consist of a low subinguinal (Marmar) or inguinal (Ivanissevich) and a high retroperitoneal (Palomo) ISV ligation (Fig 12)[90-92]. The oldest technique, the scrotal approach, has been abandoned because of high complication rates. The use of microsurgery is very useful to ligate all involved veins and to spare the arterial and lymphatic vessels. Even with microsurgery, a low ligation technique has the disadvantage that it can injure the vas deferens and deferential vessels and hence secondary testicular necrosis.

Retroperitoneal approach (Palomo)

The Palomo technique is a high retroperitoneal ligation of the ISV performed through the abdominal wall to expose and clip the dilated veins, arteries and lymphatics above the internal inguinal ring. This technique has a very low primary failure rate but a variable recurrence rate of the varicocele up to 3.4-45 % [93, 94]. Secondary failure has been attributed to the late development of venous collaterals or overlooked reno-spermatic connections. The overall complication rate of the Palomo technique is between 5-30% with a 6-10% hydrocele formation [94]. Injuries to the vas deferens, epididymitis, hematoma and wound infection are minor complications. Testicular atrophy might be a substantial risk of a lower approach in patients with insufficient arterial collaterals, for instance after prior inguinal surgery. Moreover in preexisting testicular hypotrophy semen quality can deteriorate [95].

In the modified Palomo technique the testicular artery is spared. However, preservation of the artery increases the primary and secondary failure rate (3-11%) [83] [84]. It seems that ligation of all the involved venous collaterals is more difficult to accomplish in the artery sparing technique.

Inguinal approach (modified Ivanissevich)

Through a groin incision, all distended veins (internal spermatic veins, cremasteric veins, external spermatic veins, gubernacular veins and periarterial veins (venae comitantes)) and collaterals are ligated by microsurgery at the internal inguinal ring, sparing the arterial and lymphatic vessels [96]. A prospective study by Cayanet al. compared high retroperitoneal ligation with inguinal microsurgical repair and confirmed less postoperative hydroceles (< 1%) and recurrences (2.1%) [97].

Subinguinal approach (Marmar)

Through an incision at the external inguinal ring, the spermatic cord can be reached directly. Microsurgical subinguinal approach might become the standard treatment because it seems to reduce the primary and secondary failure rate (0-2%) as well as the complication rate (1-5%) substantially [93, 98].

Laparoscopic ligation

Laparoscopic varicocelectomy is generally performed transperitoneally, but extra- or retro-

peritoneal approaches have also been described. An advantage of this technique is that ligation can be performed on a level where the ISV is separated from the testicular artery and consist of maximum two veins. Primary failure (0-11%), and recurrence rates (3-15%) are higher than in open surgery [27, 93, 99]. Like in open surgery, postoperative hydrocele can occur in up to 40% of cases [100]. Other complications of laparoscopic varicocelectomy are air embolism, nerve injuries, intestinal injury and peritonitis (8–12%)[99]. Laparoscopic varicocele ligation is more expensive, is more time consuming, requires general anesthesia and needs a longer hospital stays than open microsurgery [99].

Robot assisted varicocelectomy

Although the cost associated with a surgical robot is still a limiting factor for the widespread use, some authors report benefits compared with the conventional laparoscopic varicocelectomy [101]. An improved and more accurate micro dissection is possible by the 3-dimentional view and the better stability, freedom and ergonomics to handle the instruments.

Nowadays, inguinal and subinguinal microsurgery with lymphatic and artery-sparing techniques are the best surgical techniques to prevent high persistence rate, recurrences and postoperative hydrocele rate [98] [96] [102] [103] [104].

The choice for a high or a low inguinal approach could be based on CDUS analysis of the flow in the varicocele. This distinction is based on the classification of " stop or shunt type varicocele". If continuous reversed flow is detected after Valsalva in the PP (shunt type), a high retroperitoneal ligation could be suggested. If only a short or no reflux is observed on CDUS (stop type), a low inguinal or subinguinal approach is preferred. In such cases, Nagar et al. suggested that pelvic collateral and cross-communicating veins are responsible for the varicocele and a high ligation would have an unsuccessful outcome [105]. If this would be true, then all surgical or endovascular varicocele treatments which only target the ISV would give a recurrence in case of a shunt type. And that is not our and other's experience.

However in adolescents, shunt type is associated with more recurrences in patients treated with a retroperitoneal approach than with inguinal varicocelectomy and shunt-type has a higher risk of testicular hypotrophy among untreated patients [106].

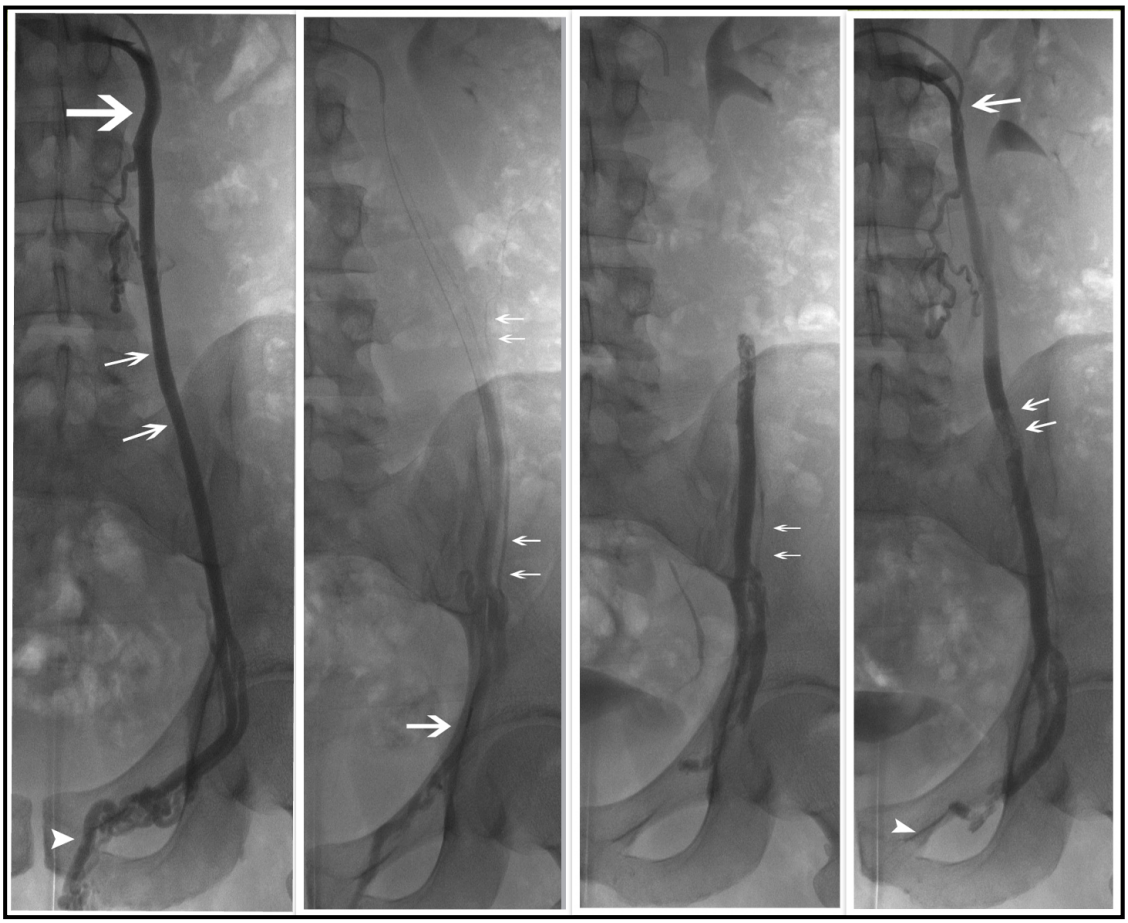
In surgery, one cause of primary failure or secondary recurrence might be the persistence of small veins around the testicular artery. These veins might communicate with the main ISV, and form a pathway for reflux to re-occur. Other causes of surgical failure are overlooked inguinal or retroperitoneal collaterals that may bypass the ligation. Also dilated cremasteric veins might be missed during laparoscopic approach.

Percutaneous endovascular occlusion

As the different surgical techniques for the treatment of varicoceles were developed in the 70-80ties, endovascular embolization emerged as a valuable alternative. Retrograde phlebography proved the existence of pathological reflux in the ISV and at the same time disclosed the pathways from the RV to the PP. Contrast visualization of the anatomy of the ISV by antegrade, but more importantly by retrograde catheterization allowed fluoroscopic controlled implantation of occlusive agents.

Fig 13: ISV embolization with glue.

Right: Selective venography in erect position with the diagnostic catheter (arrow) in the outflow of the internal left spermatic vein. Internal spermatic vein insufficiency (small arrows) is proved with visualization of the pampiniform plexus (arrowhead).
Right middle: Microcatheter (arrow) venography performed in horizontal supine position, revealed a small paraspermatic collateral (small arrows) originating from the lateral duplication of the inguinal internal spermatic vein. This anatomy forced us to reposition the microcatheter in the lateral bifurcation of the internal spermatic vein to be sure that the small collateral is also occluded during controlled injection of glue. Glue embolization will be started in the lateral branch at the level of the coxofemoral joint. During withdrawing of the microcatheter, the glue is pushed into the lateral branch, the small collateral and finally into the medial branch and the main internal spermatic vein then up to the level of the crista iliaca
Left middle: Embolization cast in the left spermatic vein with the glue located between the coxo-femoral joint and the crista iliaca including the small paraspermatic branch.
Left: Control venography with the diagnostic catheter in the internal spermatic vein (arrow) demonstrates contrast agent up to the glue cast (small arrows) and the absence of contrast to the pampiniform plexus (arrowhead).



Depending of the used embolic agent the occlusion can be restricted to the main ISV or extended to the collateral venous network. The first technique is the endovascular equivalent of the surgical ISV clipping, the latter has a similar effect of an extended microsurgical dissection and clipping of all veins. The first reports of retrograde embolization of the ISV date from the late 70ties [107] [108]. With a transfemoral Seldinger technique, a catheter is inserted in the RV for diagnostic phlebography and thereafter deep into the ISV for embolization. Embolic agents can be directly delivered through the diagnostic catheter or in a coaxial way through a microcatheter. The procedure is performed on an outpatient basis under local anesthesia on a tilted X-ray-table [109] [110].

We can distinguish liquid (sclerosing agents and glue) and non-liquid (detachable balloons, gelatin sponges and coils) agents. Many investigators use a combination of these agents to treat varicoceles. Newer products like Onyx®, vascular plugs or detachable coils are used in case reports or in unpublished series [111, 112]. Liquid agents have the advantage that they can penetrate into the collateral venous network around the ISV.

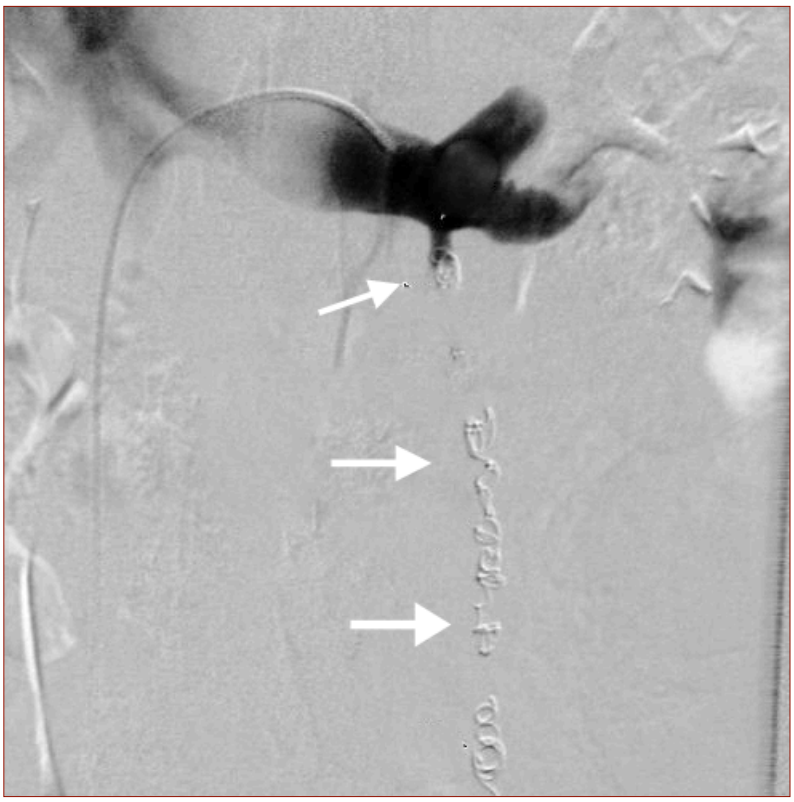
Liquid embolics

Some liquid agents like hot or boiling contrast medium and absolute ethanol proved their efficacy in experimental and human varicocele embolizations, but nowadays they are less popular agents because their injection requires general anesthesia [113, 114].

Sclerosing agents (sodium tetradecyl sulfate 3% (STS), sodium morrhuate, dextrose and aethoxysklerol (1-2 or 3 %)) are the most commonly used liquid agents in Europe (not authorized in the USA for spermatic veins). Riedl et al was the first to publish this [115]. During Valsalva maneuver, the sclerosing agent is injected as a pure liquid or mixed with air as foam at the level of the inguinal ring. Manual compression of the external inguinal ring is mandatory to prevent the agent penetrating into the PP, hence avoiding inflammation and thrombosis.

Tissue-adhesives (Cyanoacrylates) were first introduced by Kunnen et al. in 1980 [116]. Glue is a less frequently used liquid agent which requires a coaxially catheter system for application (Fig 13) [117][25, 110]. After verifying flow control with contrast agent injections during different table inclinations, the glue is sequentially injected through the microcatheter and pushed into the ISV as well into the collaterals. As soon as the glue comes in contact with blood the polymerization process starts and a permanent occlusion of the vessel occurs. The first glue used was a mixture of contrast agent and isobutyl-2-cyanoacrylate, IBCA (Bucrylate, Ethicon). Later on IBCA was replaced by NBCA (n-Butyl-2-Cyanoacrylate or Embucrilate; Histoacryl transparent, Braun, Tuttlingen, Germany) because of possible carcinogenicity [118]. Today NBCA (Histoacryl) or NBCA-MS (Glubran2, General Enterprise Marketing, Viareggio, Lucca, Italy) is used with a mixture of Lipiodol Ultrafluid (Guerbert, France) that is necessary for the fluoroscopic visualization of the glue. Both, a higher % of Lipiodol and the prior injection of glucose 10% slow down the polymerization rate.

Fig 14: ISV embolization with coils
Selective left renal venogram following left ISV transcatheter embolization shows multiple embolization coils (arrow) within the vein. Only the origin of the vein fills with contrast because there is no longer any reflux.



Onyx® (ev3, Irvine, California, USA) is a biocompatible ethylene-vinyl alcohol copolymer (EVOH) dissolved in dimethyl sulfoxide (DMSO) that in contact with blood solidifies as a kind of plastic. Onyx proved to be superior to tissue-adhesives for the occlusion and penetration of side-branches in cerebral embolization [119, 120]. Onyx embolization of varicoceles is feasible but still under investigation in our institution. Technical problems, combined with significant patient discomfort and a high radiation dose preclude at the moment its clinical use.

Non-liquid embolics

Gelatin sponge is a water-insoluble, hemostatic sponge prepared from purified porcine skin gelatin. Gelfoam may be cut in small pieces that are injected through a diagnostic catheter and is able to absorb and hold many times its weight of blood and other fluids within its interstices. Gelatin sponge is a non-permanent occlusive agent, and therefore more used in combination with other permanent mechanical or liquid embolic agents [114].

Detachable balloons can be navigated through an introducer catheter and detached in the ISV. Depending on the size of the varicocele and the presence of collateral vessels, one or more 1- or 2-mm detachable balloons are used. Riedl and White were the first to treat varicoceles with detachable silicone balloons [121] [122]. After detachment of the balloon, a single radiograph was obtained and follow-up abdominal radiographs were obtained 3 to 4 weeks after the embolization to exclude premature deflations. Balloons are frequently used in combination with other agents like coils or with "sandwiched" 70% dextrose (a sclerosing agent) [109].

Varicocele treatment with coils was introduced by Thelen et al.,who used the original 0.038-inch Gianturco coils [123]. Other fibered stainless steel coils and platinum coils were developed, which could be delivered directly or in a coaxial technique. Coils can be pushable or, to improve correct placement, also detachable. Treatment includes occlusion of the mean ISV and major branches and all accessible collaterals starting from just above the inguinal canal up to the outflow of the ISV with the RV (Fig 14).

All percutaneous endovascular techniques have a low complication rate (< 1%). Non-liquid agents (coils and balloons) and low viscosity liquids (sclerosing agents) have a high primary failure rate that ranges from 3-28 % and increases when aberrant vessels are present [122] [124]. Recurrences occur in 2-19% [125, 126] [127] [128]. Most recurrences were related to a complex venous anatomy. Only embolization with high viscosity liquids (glue) has a reported low technical failure rate (<1%) and lower recurrence rates (<2%) [24, 25, 117, 129]. The low technical failure rate is probably related to the use of a coaxial catheter system. A microcatheter with micro-guidewire facilitates to cross all competent valves. Better visualization and penetration of the embolic agent into collaterals could be responsible for the lower recurrence rate.

The need for contrast agent and the radiation exposure are the main disadvantages of the endovascular percutaneous technique. Severe allergic reactions to contrast agents are possible but very uncommon. Radiation exposure during embolization, with a subsequent 0.1% life-long risk for cancer, was reported in a retrospective study [130]. Radiation exposure during fluoroscopy is a concern but with radiation reduction techniques like lead shields and pulsed fluoroscopy, substantial reductions can be achieved.

The advantage of percutaneous embolization is that the patient can return to normal activities faster than with surgical treatment, since there is no incision and splitting of the abdominal muscles involved [70].

The retrograde technique has a higher primary failure rate with respect to surgery due to venous anatomical variations and competent outflow valves especially for right-sided varicoceles [128].

Transbrachial and transjugular approaches have been described with success after failure of the transfemoral access [131].

Antegrade embolization is normally done by injection of a sclerosing agent through an isolated scrotal vein from the PP. Antegrade sclerotherapy, first described by Tauber in 1988, can be performed by a subinguinal or suprascrotal incision close to the base of the penis [132]. Under local or general anesthesia and in a slightly anti-Trendelenburg supine position a vein of the anterior PP is cannulated with a venous catheter and after phlebography and Valsalva maneuver, a sclerosing agent is injected. However, antegrade scrotal sclerotherapy is more often used to treat persistence of the varicocele during surgery than as an initial treatment. Failure rates vary between 5-13% with more failures in patients with an initial severe reflux grade, in patients with a higher number of collateral vessels and in patients with a bilateral varicocele [133].
In our experience, we believe that retrograde liquid embolization under local anesthesia should be the treatment modality of choice for varicoceles. Solid embolic materials (metallic coils, detachable balloons) have the risk as in surgical clipping of leaving collaterals untreated, which could be responsible for recurrences. With low viscosity liquid sclerosing agents such branches and duplications can be occluded if injected in sufficient quantity and under Valsalva control. However, their low viscosity and visibility might increase nontarget embolization. Moreover, the sclerosing agent need time to obstruct the veins, so a waiting time of about 20 minutes is required to control its effect. Foam sclerotherapy and the Tessari technique improved visibility and decreased side effects [127, 134]. A higher viscosity liquid like glue has the advantage of being radiopaque and of being a quick polymerization with definitive occlusion. The polymerization time can be reduced regarding the anatomical complexity of the ISV to allow the glue to penetrate into side branches [128] [124].
In our opinion percutaneous embolization with glue should be the first line therapy in varicoceles. Superselective sclerotherapy is a good alternative in countries where tissue adhesives are not available.

Treatment for infertility

The Roman Celsus, who practiced from 25-35 AD gave us the earliest descriptions of varicocele and it's relation with fertility. He described in de Medicina: “The veins are swollen and twisted over the testicle, which becomes smaller than its fellow, in as much as nutrition has become defective.” While early varicocelectomy was performed for pain or cosmetic improvement, it was until 1952 that Tulloch detected a sperm count improvement after varicocelectomy in a patient with testicular biopsy-proven sperm deterioration [135]. Many experimental and clinical reports (randomized controlled trials (RCT) and non-RCT) prove all or not an improvement in infertility related parameters, sperm quality or PR. The wide variation in study design and the used method make it a challenge to perform a meta-analysis of RCT on the treatment of varicocele and their implications on infertility [136, 137]. Based on the current RCT's, only in infertile male with a palpable varicocele and abnormal sperm treatment seems to have and increase in sperm quality and PR [138, 139]. Therefore the current guidelines propose treatment only in infertile men with such a clinical varicocele and semen abnormalities [140]. The coincidence of additional pathology interfering with the fertility of the male or the female partner, a small total testicular volume (i.e. less than 28 ml) and very poor semen quality pretreatment decrease the probability of pregnancy [141]. The PR could increases significantly (from 29.7% to 72%) when varicocele treatment is completed with other fertility treatment like in vitro fertilization [142].

Table 6: Meta-analysis Treatment of palpable varicocele in infertile men: a meta-analysis to define the best technique. Number of included studies (N), mean pregnancy rate (PR), mean recurrence rate (RR) and mean hydrocele rate (HR) *(Cayan et al. Treatment of palpable varicocele in infertile men: a meta-analysis to define the best technique. J Androl 2009)*

Varicocele treatment option		N1	PR%	N2	RR%	HR%
Macro surgery	retroperitoneal	10	37.69	4	14.97	8.24
	inguinal	3	36	2	2.63	7.3
Micro surgery	inguinal	5	43.8	4		
	subinguinal	7	41.97	6	1.05	0.44
Percutaneous	laparascopic	5	30.07	5	4.3	2.84
	embolization	6	33	2	12.7	0

N1: all studies report data on PR
N2: studies reporting data on RR and HR

Table 7: A review of the various techniques to treat a varicocele, their results and efficacies to provide practicing urologists with some guidance for the best choice of technique. Number of included studies (N), pregnancy rate (PR), recurrence rate (RR) and hydrocele rate (HR), not available (N/A). *(Diegidio et al.. Review of current varicocelectomy techniques and their outcomes. BJU Int 2011)*

Varicocele treatment option		N	PR%	RR%	HR%
Macro surgery	retroperitoneal	4	34.21	12.5	7.58
	inguinal	6	30.06	15.65	7.47
	subinguinal	1	26.09	3.57	0
Micro surgery	inguinal	6	41.78	9.47	0.29
	subinguinal	13	44.75	2.07	0.72
Percutaneous	laparascopic	9	27.53	11.11	7.57
	embolization	7	31.93	4.29	N/A

Better understanding of which adolescent patients with varicoceles will go on to develop male infertility is necessary to identify pediatric patients who could benefit from early intervention [(143)].

However, many questioned whether varicocele repair really prevents future infertility, improves male fertility, and pregnancy rates because the majority of men with varicoceles are still fertile. Although many studies have been proposed answers, up to now there is no clear consensus, particularly in the role of repairing subclinical varicoceles. American and European urological and reproductive societies recommend varicocele treatment only for patients with clinical varicoceles and abnormal semen analysis or for adolescents with testicle hypotrophy.

Is subclinical varicocele a disease, is it significant and does it need treatment?

We know that subclinical right and left varicoceles are underdiagnosed with physical examination. It is not sure that all these positive right varicoceles diagnosed on CDUS and even on phlebography are really insufficiencies of the ISV and varicoceles. In adults we know that bilateral treatment, even with subclinical varicoceles results in better sperm, but not in better pregnancy rates. The significance, if any, of subclinical right varicoceles in adolescents is largely unknown.

In epidemiological and observational investigations, a 50% of idiopathic varicocele (including the subclinical forms) was found with Doppler ultrasound in a random male population. 3 years period observations found that subclinical varicoceles could progress to clinical varicoceles in 35%, in contrast to a healthy control group (5%). These data support that subclinical varicocele should be considered as the first stage of varicocele development and that subclinical varicocele should be diagnosed and monitored over several years, in order to identify possible alterations in testicular volume at an early stage. In our study we found arguments in the phlebographic architecture that the adolescent varicocele might be a preclinical stage of the adult, but only at the right side. Maybe we should rather think about a prophylactic treatment of adolescent right ISV insufficiency.
In adolescents we know that testicular hypotrophy in combination with a unilateral clinical varicocele results in a decrease of the sperm quality, but the incidence and effect of a bilateral varicocele on sperm quality is not know.

A recent study found no beneficial effect for treatment of clinical left varicoceles (bilateral and right varicoceles were excluded) regarding the chance of paternity later in life. The paternity rate was in both groups approximately 80%, which is a perfect fitting with the 20% of male seeking medical advice for infertility. In our phlebographic study we found for the left ISV arguments (more renospermatic bypasses, nutcracker phenomenon and more valve dysfunction) against a pure evolutive disease. These probably congenital forms of varicoceles, which are more often found in adolescents than in adults, could be a subgroup that is not responsible for future infertility. In our retrospective study we made no correlations between those specific phlebographic characteristics and sperm analyses or testicle hypotrophy. However, it would be very interesting to observe the adolescent subgroup with these probably congenital characteristics and look for further infertility. If this is not the fact, than we don't have to treat these adolescent varicoceles.

The European Association of Urology (EAU) 2014 guidelines and the American Society of Reproductive Medicine (ASRM) + the Society for male reproduction on Urology 2014 advise not to treat subclinical varicoceles in adults, even in those with abnormal sperm.The EAU and the ASRM 2014 advise not to treat adolescent subclinical varicoceles and even not to treat clinical varicoceles without hypotrophy.
So, in conclusion, 80% of patients with varicoceles have not a fertility problem and we need better selection criteria for intervention in adolescents varicoceles(subclinical and clinical) to find the 20% who will develop infertility.

Comparison of the various treatment options for a varicocele.

Each treatment technique has its own strengths and limitations and urologists, andrologists or interventional radiologists have a preference over the other for the technique in their specialty. To compare the efficacies, cost-effectiveness, recurrences and complications of the various treatment options we need well-designed large prospective randomized controlled studies. Without this, it is now today impossible to make a valid conclusion, which technique is the best treatment choice for a patient dealing with a varicocele [(144)]. In the recent literature, there are only meta-analyses, which aims to address the best treatment modality for varicocele [(102) (145) (146)].
Despite the longer surgery time and the requirement of additional surgical training, microsurgical inguinal or subinguinal varicocelectomy gives lower complication and recurrences rates [(93)].

Moreover, this kind of surgery needs a shorter hospitalization period with an earlier recovery. Meta-analyses, comparing varicocelectomy with percutaneous techniques, concluded that open, microsurgical, inguinal, or sub-inguinal techniques resulted in higher spontaneous PR, lower recurrences and complications compared with radiological embolization (Table 6 and 7) [102] [103, 104]. In these reports, embolization was considered as one group in which sclerotherapy and coil embolizations are overrepresented in the group of radiological embolization. A large well-designed prospective randomized controlled trial between the best surgical and endovascular treatment is necessary.

CONCLUSION:

Varicoceles develop on the basis of an ontogenetic disorder, valve dysfunction and external compression or a combination of it. Varicoceles are associated with male infertility. Patient's lifestyle, genetic factors and the consequences of blood reflux into the PP contribute to the infertility.

Physical examination should be combined with CDUS and thermography to establish the diagnosis of a varicocele.

Treatment of varicoceles remains controversial, particularly if the varicocele is subclinical. Inguinal or subinguinal microscopic surgery provides high pregnancy rates and low recurrence and complication rates. Endovascular embolization with glue or a sclerosans is a valuable alternative, which can easily be performed under local anesthesia and in an outpatient clinic.

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Part 3 Glue embolization in varicoceles

3.1 Glue: Its medical history and the application in varicoceles: a review.

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ABSTRACT

Since 1998, the FDA approved octyl-cyanoacrylates as a topical skin tissue adhesive. For butyl-cyanoacrylates this approval has been refused until 2007. As an endovascular adhesive and exclusive in cerebral interventions, only TRUFILL® n-Butyl Cyanoacrylate (n-BCA) Liquid Embolic System is FDA approved. GLUBRAN®2 is the only glue with a CE-mark for endovascular use.

Polymerization of glue in vessels produces an inflammatory reaction in the wall and in the surrounding tissues of the vessel, which changes in a chronic process resulting in a fibrosis. Glue has to be mixed with iophendylate, which make the mixture radio-opaque during embolization. Beside its radio-opacity, iophendylate could change the polymerization time.
Published series of varicocele treatment with glue are rare (only 9 publications). All reported a high success rate, low complication rate and low recurrence rate.

KEYWORDS: varicocele - embolization -glue

INTRODUCTION:

This review is based on the complete literature of glue used for the treatment of varicoceles.

We reviewed the properties and the history of glue: from adhesive to medical tissue adhesive and from tissue adhesive to intravascular embolic agent. The evolution of the first used intravascular glue (iso-butyl cyanoacrylate) to the recent available glues (n-butyl cyanoacrylate) is described. Biological endovascular characteristics of n-butyl cyanoacrylate are discussed. Technical aspects of how to prepare the glue, to improve radio-opacity and to change polymerization rate are explained. Finally all published reports of glue embolizations in varicoceles are discussed

BODY:

Properties and history of cyanoacrylates: from adhesive to medical tissue adhesive

Cyanoacrylates (the chemical name for glue) were discovered in 1942 in a search for materials to make clear plastic gun sights during World War 2. A team of scientists detected by accident a formula that sticks to everything that it came in contact with. After the product was rejected for this military application, cyanoacrylates were rediscovered in 1951 by Eastman Kodak researchers who recognized their true commercial potential. The "Eastman 910" was the first cyanoacrylate adhesive to be sold, in 1958. In its liquid form, cyanoacrylate consists of monomers of cyanoacrylate molecules. In the presence of water (specifically hydroxide ions) cyanoacrylate

rapidly polymerizes, forming long, strong chains. Cyanoacrylates are mainly used as adhesives, binding many surfaces almost instantly and strongly, including human skin and tissues. Cyanoacrylates were first introduced in veterinary medicine to repair bone and hide. Later on, rock climbers adapted cyanoacrylates to repair damage to the skin of their fingertips. In the "Eastman 910 adhesive" (90% methyl-2-cyanoacrylate and 10% methylacrylate) the metylacrylate was exchanged for another thickening agent because of carcinogenicity [1] [2] [3]. In a laboratory animal study, rats developed fibrosarcoma after they were exposed to methylacrylate injected subcutaneously.

The new "Eastman 910 monomer still posed problems of tissue toxicity. Applied near to small vessels, wall necrosis and thrombosis could occur [4][5]. Dr. Bernd Braun managed to develop a less toxic wound adhesive in 1964, which was first introduced under the provisional name of "Histocoll"(butyl-cyanoacrylate) and in 1968 commercialized under its definitive name of "Histoacryl" (n-Butyl-2-cyanoacrylate, Braun Germany). Although cyanoacrylate spray was used successfully by the American medics in the Vietnam War to retard bleeding in wounded soldiers, it was not approved for covering wounds and skin defects by the FDA afterwards.

N-Butyl-2-cyanoacrylate (NBCA, Enbucrilate) has been used for medical and veterinary indications since the 1970's. It polymerizes rapidly in monomer form in presence of ionic substances like moisture, blood or tissue fluids. The polymerized form has excellent tensile strength and is very effective in closing surgical incisions. In wound closure cyanoacrylates are bacteriostatic, painless and safer than traditional suturing [6]. However, because of the inflammatory reaction and intrinsic risk of skin irritation, the FDA did not approve the original cyanoacrylates as a medical adhesive until 1998. After the butyl group was extended to an octyl group (Dermabond), the FDA withdrew its objections and approved cyanoacrylates as a topical skin tissue adhesive. In 2007 also Histoacryl was approval for this indication [7].

From tissue adhesive to intravascular embolic agent

Hoppenstein and Goetz detected fusiform dilatation, thrombosis and finally necrosis of the vessel wall after application of the "Eastman 910 monomer" on small bloodvessels in animal experiments [8, 9]. Already in the early days of transcatheter embolization, radiologists thought of using tissue adhesives to occlude blood vessels permanently. The endovascular application of glue was accelerated by the need for improving treatment of cerebral arteriovenous malformations (c-AVM). A treatment of a c-AVM requires occlusion of the nidus. A liquid embolic agent such as glue is able to penetrate into the nidus and by it controlled polymerization to occlude the nidus instantaneously. During 2 years, Kerber et al. experimented with isobutyl-2-cyanoacrylate (IBCA) (Ethicon Corp, Somerville, NJ), which has a lower viscosity and a faster polymerization time than the other available tissue adhesives [10]. After Zanetti et al. occluded animal aneurysms with IBCA, Kerber et al. treated inoperable arteriovenous malformations in 3 patients with partial success [11] [12]. After neurosurgical extirpation, histopathology showed a mild tissue reaction limited to a loss of intima with minimal changes seen in the media. The occlusive effect of the adhesive was satisfactory both on angiographic follow-up and microscopic evaluation. In the same year Dotter et al. published successful occlusion of renal and pelvic arteries, both in a life-threatening situation [13]. Many tissue adhesives were developed for endovascular applications. The first successful one was Bucrilate or isobutyl-2-cyanoacrylate (IBCA). The company Ethicon withdrew this glue from the market in the mid 80's because of possible carcinogenicity.
According Ethicon, a study designed to evaluate the long-term effect of chronic intraperitoneal

Fig 1: Chemical structure of n-butyl 2-cyanoacrylate (Histoacryl®)(2D and 3D)

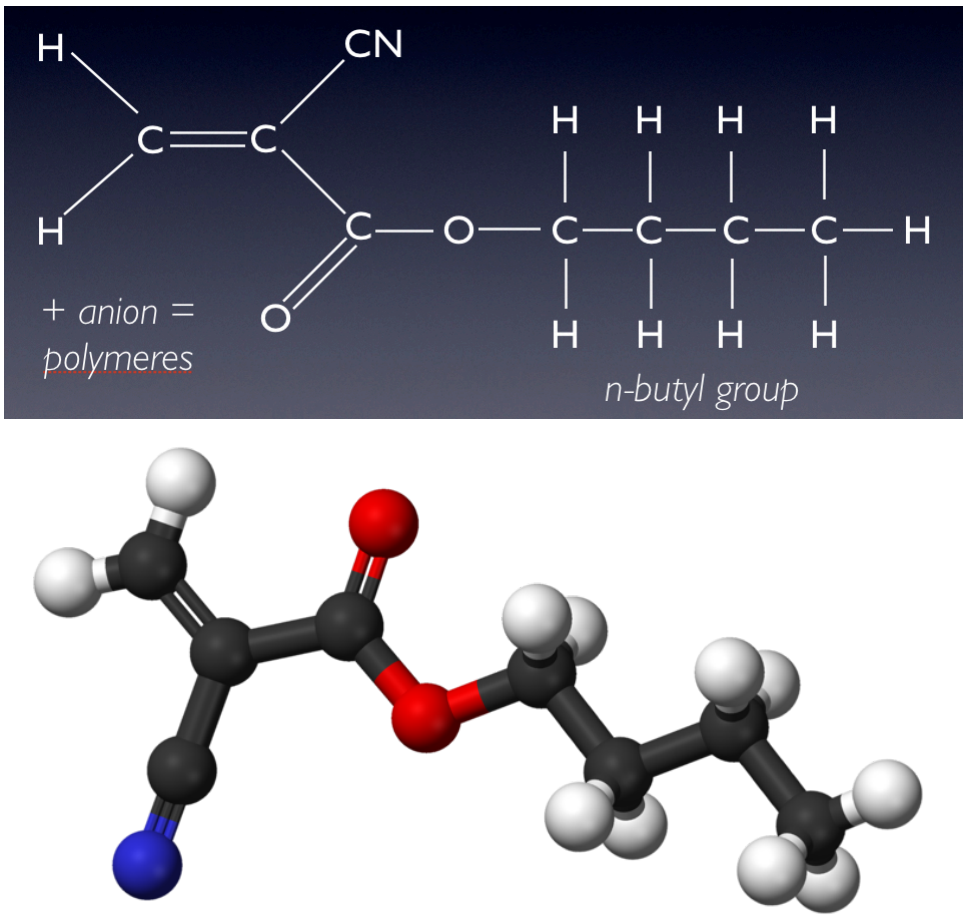


Fig 2: Chemical structure of Glubran 2®

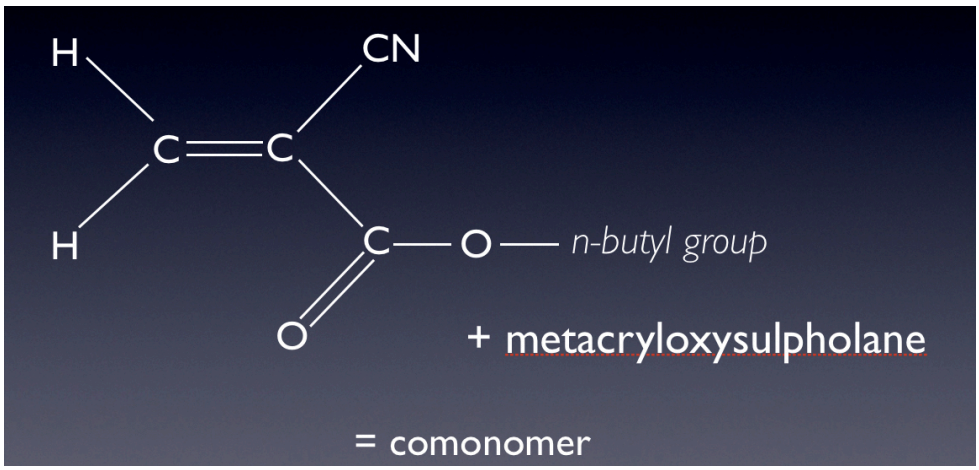
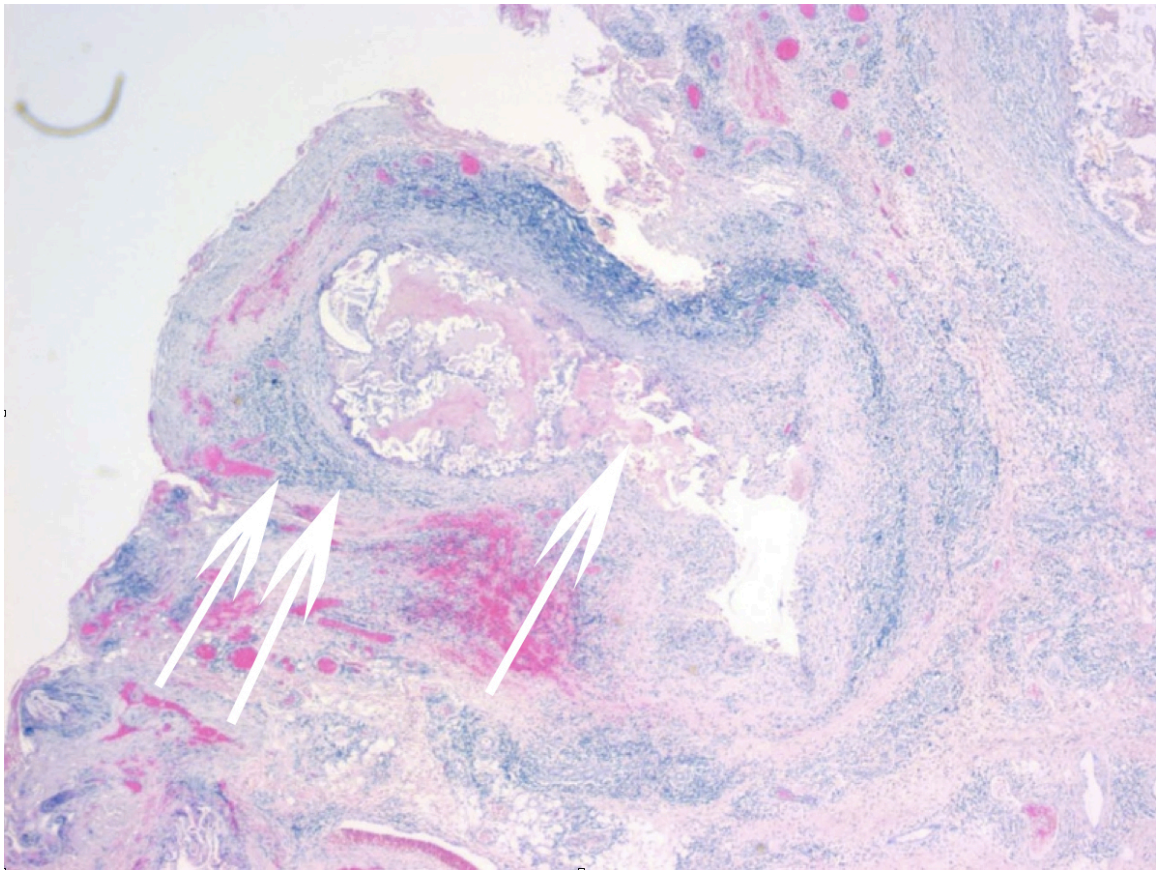


Fig 3: Histology of an extracranial AVM after pre-surgical embolization with glue (courtesy Dr. C. Vandenbroecke, Department of Histopathology, Ghent University Hospital). There is a massive lymphocyte infiltration in the vessel wall (double arrows) after glue occluded the nidal vessel (arrow).



implantation of IBCA in the rat suggested strongly a dose-related carcinogenic potential.
This study was never published and therefore criticized by interventional radiologists and glue adepts [14][15][16].
Nevertheless, IBCA was substituted by NBCA (N-butyl 2-cyanoacrylate or Embucrilate), which proved to be a safe and effective alternative embolic agent for AVM's [17](Fig 1). Different companies distributed this tissue adhesive under different names. Histoacryl (Histoacryl, Braun, Tuttlingen, Germany) is manufactured as Histoacryl "transparent" and Histoacryl " blue". In the latter, a dye "methylene blue" is added for better tissue visualization for surgical and non-endovascular use. NBCA is also available as " Trufill " (Codman Neuro, Raynham, Massachusetts, USA) but manufactured not as a liquid but as particles. "Avacryl" (Tripoint Medical, Raleigh, USA) was withdrawn for medical use in 1992 for unknown reasons.
In an attempt to improve the control of the polymerization, to reduce the inflammatory reaction and the risk of catheter gluing the butyl group was replaced by a longer carbon group (2-hexyl-cyanoacrylate, Neuracryl M (Prohold Technologies, El Cajon, California). The PROVASIS trial could have proven its value in embolization of c-AVM, but the trial was stopped for financial reasons [18]. Nevertheless, n-hexyl-cyanoacrylate is still available as Purefill® (Fimed, Quincie-en-beaujolais, France). In an animal study by the group of Vidal et al. (Marseille, France) communicated on the internet, catheter adhesivity of the purefill glue was lower, but the inflammatory reaction the same as the classical cyanoacrylates.

Another attempt to alter the polymerization properties of NBCA was the addition of a monomer 'metacryloxysulpholane' produced by the General Enterprise Marketing company.
The company replaced its original slower polymerizing Glubran (Ethyl-2-Cyanoacrylate + Butylacrylate + Methacryloxysulfolane) for the faster and more stable polymerizing Glubran2 by exchanging the ethyl for n-butyl and omitting butylacrylate [19].
This NBCA with a co-polymer (NBCA-MS) is on the market since 2002 (Fig 2). Neither the chemical formula of metacryloxysulpholane, nor the reaction to form a co-monomer or polymers is published by the company. Solfolane (2,3,4,5-tetrahydrothiophene-1,1-dioxide) should be the solvent. The company claimed that the additional monomer should be responsible for a slightly longer polymerization time, a lower exothermic reaction (45°) and a lower histotoxicity producing less inflammatory reaction [20].

Availability of glue

NBCA (Histoacryl, Braun) has no CE mark for surgical or endovascular procedures. Moreover, in the providers leaflet, it is clearly noted that Histoacryl is contra-indicated for endovascular applications in Europe. NBCA (Trufill, Cordis) has only FDA approval for the presurgical devascularization of c-AVMs in the USA. Trufill will probably replace Histoacryl for peripheral applications in the USA. Why Braun did not made efforts to obtain for Histoacryl an approval for endovascular use in Europe remains unknown. NBCA-MS (Glubran-2, GEM) has a CE mark, indicating that the product complies with the essential requirements of the applicable European laws or Directives with respect to safety, health, environment, and consumer protection and it is authorized for surgical and endovascular procedures. Glubran-2 has no FDA approval. 2-Hexyl-cyanoacrylate is only available as Purefill®, (Fimed) and has a CE approval as a surgical and tissue glue for internal use and as a liquid embolic agent.

Biological endovascular characteristics of n-butyl cyanoacrylate

After contact with blood-ions, n-butyl-cyanoacrylate polymerizes in long and stable chains of cyanoacrylates. The polymerization produces an exothermic reaction (ranging from 33-76°), resulting in limited thermal damage of the vessel. During deposition of cyanoacrylate within a vessel, a biological degradation of formaldehyde and alkyl cyanoacetate occurs. These degradation products cause an acute inflammatory reaction in the wall and in the surrounding tissues of the vessel. After 1 month the inflammatory reaction changes in a chronic and granulomatous process with appearance of foreign body giant cells and massive lymphocyte infiltration resulting in a fibrosis (Fig 3) [17].

Technical aspects to use n-butyl cyanoacrylate

Radio-opacity

n-Butyl cyanoacrylate, in his pure form is not visible under fluoroscopy. To increase radio-opacity during embolization powered metals like tantalum and tungsten has been added. These opacification agents particulate and settle out quickly to the bottom of the syringe and there fore the mixture had to be injected quickly. Cromwell et al. experimented with iophendylate, an iodized oil and found that a 50% mixture with NBCA provide a satisfactory and stable opacification [21][22]. Beside its radio-opacity, iophendylate could change the polymerization time. To delay the polymerization time, the % of iodized oil (1/1-1/4) has to be increased in the mixture. Other investigators attempted to delay the polymerization by uploading first the catheter with dextrose 5% to 50% [11][23]. Also glacial acetic acid, which decreases the pH (which is also the case with tantalum and tungsten) can be used to delay the polymerization time [24][25].

Glue preparation.

In a 3 or 5 cc syringe, 1or 2 cc of lipiodol Ultrafluid ® (Guerbet, France) is aspirated and mixed with 1or 2 cc of n-butyl-cyanoacrylate (Glubran2) respectively. The used quantity of glue and the proportions n-butyl-cyanoacrylate /lipiodol depends on the anatomy of the ISV. We usually embolize with a 1 to 1 proportion n-butyl-cyanoacrylate /lipiodol. Rarely more than 2 ampules, i.e. 2 cc of n-butyl-cyanoacrylate, are necessary. A 3cc syringe is filled with 10% glucose and connected to a plastic 3-way stopcock of the microcatheter, which itself is filled with 5% of glucose. A second syringe with the mixture "n-butyl-cyanoacrylate /lipiodol" is connected to the 3-way stopcock, in order to inject into the microcatheter.

Tissue-adhesives for the treatment of varicoceles

Kunnen introduced in 1980 the use of IBCA in varicocele treatment [26]. He reported a relative simple, safe and successful coaxially method to occlude the ISV in 35 patients on an outpatient basis. The microcatheter was brought caudal to the lowest anastomosis between the ISV and the perirenal venous plexus and preferably superior to any bifurcation. After the tilting table was inclined so that flow stops in the ISV, the microcatheter was filled with 5% glucose and a tuberculine syringe was prepared with a maximum of 0.6 ml of IBCA in between 0.1 ml 60% contrast agent. Quickly the glue was injected through the microcatheter and blindly pushed into the ISV with 0.7 ml 10% glucose through a plastic 3-way stopcock on the microcatheter. The microcatheter was pulled back 2 to 3 cm and flushed completely with the residual 0.3 ml 10%

glucose. Today NBCA (Histoacryl) or NBCA-MS (Glubran2, General Enterprise Marketing, Viareggio, Lucca, Italy) are mixed with Lipiodol Ultrafluid (Guerbert, France) for the radio-opacity. Lipiodol does not initiate polymerization like contrast agents, which made the preparation of the glue easier than in the past.

Since Kunnen published its first 35 patients in 1980, few additional series of varicoceles, embolized with glue were published to date (Table 1).

In 1985, Kunnen described a technical success of more than 99 % in 435 patients, 0.46% complications (two glued catheters) and recurrences in 1.6 % [(27)]. In men with normal testicular volume, decreased follicle stimulated hormone below the average and a moderate impairment of the spermatogenesis, there was a pregnancy rate between 60 and 80%. Only Kunnen used IBCA until it was taken off the market in 1985. Since then, only studies of spermatic vein embolizations with NBCA or NBCA -MS or the combination of the two were published. First, a German group from Berlin embolized 30 patients with NBCA mixed with Lipiodol with a technical success of 100 % and a recurrence rate of 6 % [(28)]. More recent reports showed a very high technical success (100 %), very few complications (0-1.2 %) and low recurrences (0-2.1 %) [(29)] [(30)] [(31)] [(32)].

Two studies reported a higher recurrence rate of 6% [(33)(34)]. Although we expect some inflammatory reaction of the glue, thrombophlebitis of the PP is rarely reported [(33)]. We think that a mild thrombophlebitis is present in most of the patients with a minimal self-limiting discomfort. Other patients have a mild to moderate pain reaction during the week after embolization localized in the abdominal flank, probably reflecting thrombophlebitis of the embolized ISV (not at the PP) [(35)].

Most of the investigators choose a 1/1 glue-lipiodol mixture to obtain a rapid polymerization and avoid penetration of the glue into the PP.

The largest population of varicoceles embolized with glue to date (3043 patients) is described by Kunnen in a book chapter. He reported a very low technical failure (<1%), a low complication rate (0.3 %) and recurrence rate (2 %) and a high pregnancy rate (50%) [(36)].

Table 1: Published series of varicoceles treated with glue

	N (pt)	Tissue-adhesive	glue/ lipiodol	Technical failure	Technical complications	Clinical complications (mild to moderate discomfort)		Recurrences	Pregnancy rate
						during embolization	1 wk after embolization		
Kunnen'80	35	IBCA	NA	0%	2.8% (1glued catheter)			0% (PE+T+ CDUS)	NA
Comhaire '85	97	IBCA	NA	0%	NA			0% (PE+T+ CDUS)	50.5%
Mansfeld '86	30	NBCA	NA					3% (1pt on PE)	
Nieschlag '93	33	NBCA	NA					6 % (2pt)	33% (12months)
Heye '06	64	NBCA-MS (32) NBCA (32)	1/0.8 1/0.8	0%	17% (11 perforations)	3.28 NBCA-MS 3.23 NBCA***		2.1% (1pt)	
Sze '08	9 8	NBCA NBCA+coils	1/3*	0%		5.9% (thromboplebitis		5.9%	
Vanlangenhove '12	83	NBCA (54) NBCA-MS (58)	1/1.2 1/1	0%	1.2 % (1 acute allergic reaction)	48% NBCA 38% NBCA-MS	57% NBCA 60% NBCA-MS	0	
Pietura '13	17	NBCA	1/1	0%**	0%	100%	17.6%	0 % (3months/CD US)	
Urbano '14 ****	41	NBCA-MS	1/1	0%	0%	NA	17%	0 % (12 months PE+CDUS)	

NA: Not available
*: Ethiodol
**: only phlebographic control in 3 of the 17 patients
***: mean VAS pain score
****: no coaxially catheter system / all patients took NSAID during 3 days
italic: same patient group

PE: physical examination, T:thermography, CDUS: color doppler ultrasound

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3 Aims of the work

Aims of the work

General objectives:

This work aims to contribute to the pathophysiology and treatment of varicoceles. The research project is mainly clinical and encompasses 5 prospective studies and 1 retrospective study of patient populations from the Ghent University Hospital, Belgium.

1. To assess the endovascular treatment of varicoceles by liquid embolization.

2. To contribute to the understanding of the pathophysiology of varicoceles.

Specific objectives:

3. To assess the safety and efficacy of two types of glue for embolization of varicoceles.

4. To assess the tolerance of two types of glue for embolization of varicoceles.

5. To assess the safety, efficacy and tolerance for a non-gluing liquid embolic agent, in the endovascular treatment of varicoceles.

6. To assess radiation burden for patient during varicocele embolization.

7. To develop a standardized method to read the phlebographic anatomy of varicoceles

8. and to find arguments for a different ontogenesis of varicoceles in adolescents and adults

9. To develop a standardized method to measure the intravascular pressure in the internal spermatic vein

10. and to find out whether infertility in varicoceles can be explained by the principle of elevated hydrostatic pressure.

4. Results

4. Part 1 Endovascular treatment of varicocele with viscous liquid embolic agents

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CLINICAL INVESTIGATION VENOUS INTERVENTIONS

Efficacy and Safety of Two Different *n*-Butyl-2-Cyanoacrylates for the Embolization of Varicoceles: A Prospective, Randomized, Blinded Study

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Abstract
Purpose This was a prospective, randomized, blinded comparative study of the efficacy and safety of two different *n*-butyl-2-cyanoacrylates (NBCAs) for embolization of varicoceles.
Methods A total of 112 insufficient spermatic veins (left-sided, $n = 84$; right-sided, $n = 28$) that were diagnosed in 83 adult males were prospectively randomized for blinded embolization with NBCA ($n = 54$; Histoacryl, Braun, Germany) or NBCA-MS ($n = 58$; Glubran2, General Enterprise Marketing, Viareggio, Lucca, Italy). Handling, embolic efficacy, and safety of both NBCAs were compared according the fulfillment of a standardized embolization plan, the occlusive effect on the spermatic vein, and the sticking to the microcatheter. Statistical analysis was performed with the Mann–Whitney *U* test and the Fisher's exact test.
Results Patients of both study arms were comparable for age and clinical indication. Spermatic vein characteristics were comparable for varicocele classification and embolization side. Both NBCAs were equally efficient in occluding the spermatic vein and blocking reflux (NBCA, $n = 54/54$, 100% vs. NBCA-MS, $n = 54/57$, 94.7%; $P = 0.244$). The embolization plan could be accomplished in an equal number of veins for both groups (NBCA, $n = 45/54$, 83.3% vs. NBCA-MS, $n = 41/58$, 70.7%; $P = 0.124$). Adhesiveness of the glue to the microcatheter was the same in both NBCA groups (NBCA, $n = 25/54$, 46.3% vs. NBCA-MS, $n = 29/58$, 50%; $P = 0.71$). No glue-related complications were noted.
Conclusions NBCA and NBCA-MS are equally efficient and safe glues for embolization of varicoceles.

Keywords Varicocele · Embolization · Tissue adhesives

Introduction

Varicoceles are abnormally dilated veins in the pampiniform plexus that are caused by reflux of blood in the internal spermatic vein [1]. The incidence of varicoceles is approximately 15% of the adolescent male population and rare before the age of 10 years [2, 3]. In up to 45% of infertile males, varicocele is observed [4].

The etiology of varicoceles is probably multifactorial. Anatomical variations of the internal spermatic vein, internal spermatic reflux secondary to congenital and/or acquired valve dysfunction [5], and left renal venous obstruction by the "nutcracker effect" [6] are among the most accepted.

Treatment is indicated because of local discomfort, prostatovesiculitis, sexual inadequacy, or male infertility and reduced sperm quality [7–9]. Treatment consists of interruption of reflux through the internal spermatic vein and its branches superior to the pampiniform plexus. This can be achieved by surgical or percutaneous endovascular techniques. Percutaneous embolization has the advantage

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Preface to part 1.1

In the 70-80ties, endovascular treatment of varicoceles emerged as a valuable alternative for surgery. Many investigators used non-liquid agents (detachable balloons, gelatin sponges and coils) and liquid agents (sclerosing agents and glue). Since 1985 at the department of Interventional Radiology, we have been using almost exclusively the tissue-adhesive "Histoacryl transparent" (NBCA, n-Butyl-2-Cyanoacrylate or Embucrilate; Histoacryl transparent, Braun, Tuttlingen, Germany) with success.
In 2001, an alternative, but chemical very similar, tissue-adhesive was introduced under the name " Glubran®2 " (Glubran2, NBCA-MS, n-Butyl-2-Cyanoacrylate-methacryloxysulfolane, General Enterprise Marketing, Viareggio, Lucca, Italy).
The company promoted Glubran2 because of a higher stability combined with the same occlusive capacities as NBCA [(1)]. This should result in a more controllable embolization. In practice, and especially with our modified technique of embolization, this could lead to a better consistent filling of the main branch of the ISV and to a better penetration of the glue into the side-branches.

No controlled study proved the clinical superiority of the newer NBCA-MS over the classical NBCA. If we could prove that NBCA-MS has the same handling and occlusive capacities and is equally safe, it would be preferable to swap NBCA for NBCA-MS. NBCA-MS has a CE approval for endovascular use, which is not the case for NBCA.

To clarify this issue, we initiated a blinded comparative prospective randomized study in terms of handling, efficacy of embolization and safety of both NBCAs (aim 1&3). As a model, we choose the insufficient ISV, in which I have a long experience using the classical NBCA.

Since we expected a very high technical success for both glues, we explored other parameters to compare the two glues occlusive effects. For each embolization, an embolization plan was noted in advance, depending on the anatomy of the ISV. This plan consisted of four steps or conditions that had to be technically achieved during embolization. If three out of the four conditions were met, the embolization was accepted as efficient and sufficiently controllable.

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4. 1.1 Efficacy and safety of two different n-butyl-2-cyanoacrylates for the embolization of varicoceles: a prospective, randomized, blinded study.

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ABSTRACT

PURPOSE: A prospective randomized blinded comparative study of the efficacy and the safety of two different n-Butyl-2-Cyanoacrylates (NBCAs) for embolization of varicoceles.

MATERIALS AND METHODS:
N=112 insufficient spermatic veins (left sided N=84, right sided N=28) diagnosed in N=83 adult males were prospectively randomized for blinded embolization with either NBCA N=54 (Histoacryl, Braun, Germany) or with NBCA-MS N=58 (Glubran2, General Enterprise Marketing, Viareggio, Lucca, Italy). Handling, embolic efficacy and safety of both NBCAs were compared according the fulfillment of a standardized embolization plan, the occlusive effect on the spermatic vein and the sticking to the microcatheter. Statistical analysis was performed with the Mann-Whitney U-test and the Fischer's exact test.

RESULTS:
Patients of both study arms were comparable for age and clinical indication. Spermatic vein characteristics were comparable for varicocele classification and embolization side. Both NBCAs were equally efficient in occluding the spermatic vein and blocking reflux (NBCA N=54/54, 100% versus NBCA-MS N=54/57, 94.7%; P = 0.244). The embolization plan could be accomplished in an equal number of veins for both groups (NBCA N=45/54, 83.3% versus NBCA-MS N=41/58, 70.7%; P =0.124). Adhesivity of the glue to the microcatheter was the same in both NBCA groups (NBCA N=25/54, 46.3% versus NBCA-MS N=29/58, 50.0%; P=0.710). No glue-related complications were noted.

CONCLUSION:
NBCA and NBCA-MS are equally efficient and safe glues for embolization of varicoceles.

KEYWORDS: Varicocele / Embolization / Tissue-adhesives

INTRODUCTION

Varicoceles are abnormally dilated veins in the pampiniform plexus [1], caused by reflux of blood in the internal spermatic vein. The incidence of varicoceles is about 15% of the adolescent male population [2] and rare before the age of 10 years [3]. In up to 45% of infertile males varicocele is observed [4].
The etiology of varicoceles is probably multifactorial. Anatomical variations of the internal spermatic vein, internal spermatic reflux secondary to congenital and/or acquired valve dysfunction [5] and left renal venous obstruction by the "nutcracker effect" [6] are among the most accepted.
Treatment is indicated because of local discomfort, prostatovesiculitis, sexual inadequacy or male infertility and reduced sperm quality [7] [8] [9]. Treatment consists of interruption of reflux through the internal spermatic vein and its branches superior to the pampiniform plexus. This can be achieved either by surgical as by percutaneous endovascular techniques. Percutaneous embolization has the advantage of being an outpatient procedure with a faster return to normal activities [10] and a considerable lower cost and lower recurrence rates [11] [12] than surgery. Embolization materials like stainless steel coils [13] [14], detachable balloons [15] or sclerosal agents [16] [17] were used.
The use of the tissue adhesive IBCA (Isobutyl-2-Cyanoacrylate, Bucrylate, Ethicon) in varicocele was initiated by Kunnen in 1980 [18]. Later on IBCA was replaced by NBCA (n-Butyl-2-Cyanoacrylate or Embucrilate; Histoacryl transparent, Braun, Tuttlingen, Germany) [19] by reasons of possible carcinogenicity [20] [21]. Despite excellent embolization results in arteries and veins, NBCA never received a CE-label for intravascular use. NBCA distributed as Trufill [22] (Johnson&Johnson, Langhorne PA, USA) was recently approved by the Food and Drug Administration (FDA) for the preoperative embolization of intracranial arteriovenous malformations.
After contact with blood-ions NBCA forms long and stable chains of NBCA, the so-called polymerization. The polymerization produces an exothermic reaction (ranging from 33-76°), resulting in limited thermal damage of the vessel. The intravascular temperature may vary depending on the temperature of the cyanoacrylate-lipiodol components, on the different concentration of this two components, on the amount of 10% dextrose injected and, finally, on the ionic blood charge. Degradation products as formaldehyde and alkyl cyanoacetate cause an acute inflammatory reaction, in the vessel wall and in the surrounding tissues [23], followed by a chronic granulomatous inflammation, which finally results in fibrosis [19].

In 2001, a new tissue adhesive consisting of the same monomer as NBCA (n-Butyl-2-Cyanoacrylate) but with addition of a co-monomer (Methacryloxysulfolane) came on the market as Glubran2 (NBCA-MS) by General Enterprise Marketing (Viareggio, Lucca, Italy) [24]. The company replaced its original slower polymerizing Glubran (Ethyl-2-Cyanoacrylate + Butylacrylate + Methacryloxysulfolane) for the faster and more stable polymerizing Glubran2 by exchanging the ethyl for n-butyl and omitting butylacrylate [24]. According to the manufacturer, NBCA-MS should have the same embolic capacities as NBCA. Because the induction of the polymerization process is different (non-anionic and reaches max 45°) the NBCA-MS polymer would be more stable and hence the embolization more controllable and the inflammatory reaction less pronounced. Preliminary research pointed indeed at a lower histotoxicity and diminished inflammatory reaction [25]. Moreover, unlike NBCA, NBCA-MS has a CE-approval for endovascular use.
Because we lack any study proving superiority of the newer NBCA-MS over the classical NBCA

in terms of handling, efficacy of embolization or safety, we initiated a blinded comparative prospective randomized study with both NBCAs. As a model, we choose the insufficient spermatic vein in varicoceles.

MATERIALS AND METHODS

Patient's selection criteria

From December 2006 until November 2008, 238 patients were referred for varicocele embolization to our department. Only adult patients referred for primary varicocele treatment were eligible for inclusion. Excluded were patients younger than 18 years (N=45), patients who were unable to understand the informed consent (N=11) or who had a previous treatment (endovascular or surgical) (N=5). Excluded post hoc from evaluation were patients with a normal phlebogram (N=5), or with veins unsuitable for embolization with glue (N=13) or patients who could not be treated because of technical failure (N=1) or patients with an early complication (N=1). Twelve patients refused to participate in the study. The other 62 patients were not included because they presented at a time when the study-operator was not available for the study. Finally, 83 patients could be included, in whom 112 spermatic veins were found to be insufficient and hence eligible for treatment and randomization. All individual spermatic veins were planned for a single injection embolization except if a duplicated spermatic vein was present. In such cases, the concept was to embolize each vein separately but with the same glue (and same allocation number) and let it count for two embolizations. If a single vein required two injections for occlusion, then we also counted an extra embolization. Therefore, the number of left spermatic vein embolizations might exceed the number of treated patients. Randomization was applied on each left and/or right insufficient vein prospectively on a basis of intention to treat. In the same patient, the left varicocele could be randomized to a different embolic agent than the right one. The study was approved by the ethical board of our hospital.

Comparability of both study populations

To exclude patient related bias we compared age, clinical indication, side of embolization (left/right), clinical and phlebographic classification of the varicocele between both NBCA groups. Impotence, clinical inconvenience with or without infertility, primary or secondary infertility and prophylactic embolization were reasons for treatment, thus reflecting clinical indication. Varicoceles were classified according an adapted version of Dubin and Amelar [26] in subclinical, grade 1 (small), grade 2 (moderate) and grade 3 (large). Phlebographic classification of the left spermatic vein insufficiency was done according the Bähren types [27] [28] and for the right spermatic vein according Siegel [29].

Fig 1 Selective venography in supine position with the microcatheter (double small arrows) in a distal left spermatic vein to visualize all collaterals. Injection of glue will be started from the tip of the microcatheter just at the level of the coxofemoral joint (double small arrows) (distal starting point) up to the level of the crista iliaca (small arrow) (proximal ending point). In this way, all the medial paraspermatic branches will be blocked (arrowheads).

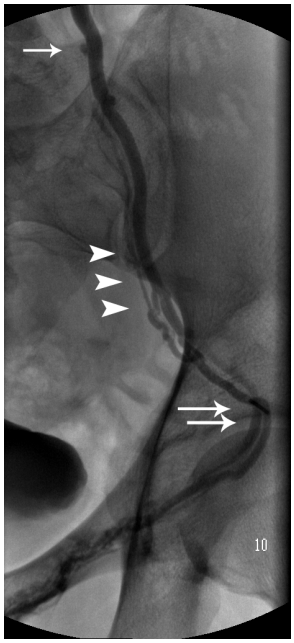

Fig 2: Embolization of the left spermatic vein.The glue is located between the coxo-femoral joint and the crista iliaca including the medial paraspermatic branch, but is inhomogeneous (arrowheads) distributed at the middle of the embolus (step 2 of the embolization plan not fulfilled).

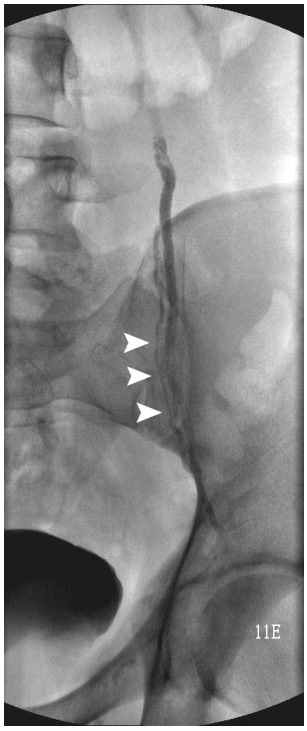

Fig 3: Control venography with the diagnostic catheter (which is not occluded) in the internal spermatic vein demonstrate the absence of visualization of the pampiniform plexus (arrowheads). 3 of the 4 conditions of the embolization plan are achieved in this patient.

Retrograde venography and superselective coaxial catheterization of the internal spermatic vein

After extensive local anesthesia with Lidocaine 1% (Xylocaine NV Astra Zeneca, Brussels, Belgium), right transfemoral selective venographies of the renal veins and the internal spermatic veins were performed using 6 French (F) diagnostic catheters (Cobra-shaped and a Simmons 1 catheter respectively for the left and the right internal spermatic vein; Cook Europe, Bjaeverskov, Denmark). The studies were done in anti-Trendelenburg position on an Iconos R 200 tilt table (Siemens, Erlangen, Germany) under Valsalva manoeuvre with a maximum of 50 cc contrast-agent (Visipaque 270 mgI/ml, GE Healthcare, Wemmel, Belgium).
Venous insufficiency was substantiated by retrograde opacification of the spermatic vein and of the plexus pampiniformis, either spontaneously or after passing a competent valve. Proximal competent valves were usually crossed with the diagnostic 6F catheter, distal valves with a 3F Microferret microcatheter (modified coaxial infusion set with slip-coat hydrophilic coating; Cook Europe, Bjaeverskov, Denmark) during coughing or Valsalva manoeuvre. The microcatheter was then positioned supra-inguinal to perform a superselective distal venography in supine position. Paraspermatic veins, connecting collaterals or renospermatic bypasses to the internal spermatic vein were mapped (fig 1).

Embolization technique with a tissue adhesive

The aim of embolization was to occlude the spermatic vein along with the parallel and segmental veins, covering the origins of all relevant side-branches or renospermatic bypasses. The level of achieved microcatheterization determined the technique of glue injection. If the microcatheter could be advanced distally to the lowest side-branche or renospermatic bypass, called the "distal embolization starting point" (usually at the level of the coxofemoral joint), and table tilting established flow control, then the glue was pushed out to fill up the main vein and to plug the distal side-branches. Then the microcatheter was withdrawn slowly while continuing glue injection until all relevant proximal branching points were covered ("proximal embolization stop point") (fig 2). If the ideal "distal embolization starting point" could not be reached (due to tortuosities or anatomic variations), then increased tilting in combination with preloading of the distal vein with glucose 10% (a higher glucose concentration to slow down the polymerization) should enable propelling of the glue embolus beyond the postulated "distal embolization starting point". Once the glue column reached the tip of the microcatheter, we continued the embolization in the way as described above.
At the end of the embolization, patency of the diagnostic guiding catheter and the microcatheter were noted. Ten minutes after embolization, a control venography of the internal spermatic and the renal vein in a tilted table position and during Valsalva manoeuvre should confirm obliteration of the spermatic vein and collaterals (fig 3). If residual reflux was observed, a new microcatheter was introduced to finish the embolization with the same glue.

Randomization and blinded set-up

Randomization was done by a computer ad random program producing a continuous list of "0 "(NBCA) and "1" (NBCA-MS) numbers. Each spermatic vein was allocated to one number on the list on a basis of intention to treat. If the vein was insufficient, it was embolized with the allocated glue, prepared concealed from the investigator by a technical assistant in a separate room. In a 3

ml syringe, either 1 cc of NBCA or 1 cc NBCA-MS was mixed with 1.2 cc or 1.0 cc of Lipiodol Ultra-fluide (Liopidol Ultra-fluide, Laboratoire Guerbet, Roissy, France) respectively. The decision to utilize a mixture with a higher concentration of NBCA-MS was empirical based on the supposed slower polymerization rate of Glubran2 [25]. In a non-controlled pilot study of 30 embolizations, we tested Glubran2 in this concentration and found the dilution appropriate. The operator received a 3 cc syringe filled with 1.8 cc of the allocated glue mixture, which had always the same odor or color irrespective of the tissue adhesive. All embolizations in the study were done by the same experienced operator.

Efficacy of the tissue adhesive

Technical success was defined as an occlusion of the internal spermatic vein and no reflux of contrast medium to the pampiniform plexus as confirmed by control venography after 10 minutes in reversed Trendelenburg position and during Valsalva manoeuvre. Because we expected that glue embolization would be successful eventually in most patients, we looked for subtle parameters to assess and compare the handling and safety of each glue. For each single embolization act an "embolization plan" was conceived, consisting of 4 steps: (1) formation of a glue embolus between the postulated distal embolization starting and proximal embolization ending point, (2) formation of a continuous and homogeneous embolus, (3) occlusion of the main and parallel veins and relevant side-branches in one single continuous injection and (4) the preservation of the patency of the guiding catheter, defined as spontaneous aspiration of blood from the catheter.
Step 1 will check whether the glue tends to migrate too distally into the pampiniform plexus or tends to reflux early in the main spermatic vein (inadequate distal side-branche occlusion, non-target embolization of the renal vein).
Step 2 checks whether the embolus is spread out or fragmented by residual blood flow, reducing the occlusive effect. Migration of embolus parts proximally would incline the operator to withdraw the microcatheter prematurely to prevent catheter gluing.
Step 3 evaluates whether the distinct amount of glue in combination with the described technique is appropriate for a single step embolization (cost and radiation-reduction). We decided that this step was not completed when side-branches or parallel veins were not filled up with glue as was planned before. This did not mean that on control phlebography reflux to the plexus pampiniformis could be confirmed in all these cases.
Step 4 checks whether glue droplets in the vein, around the guiding catheter or at the microcatheter cause obliteration of the guiding catheter at time of withdrawal of the microcatheter (necessitating insertion of a new catheter for control venography, occasionally failing to enter the spermatic vein again due to spasm of a competent valve).
We postulated that at least 3 of the 4 steps of the "embolization plan" must be fulfilled to accept a well-controlled and efficient procedure.

Table 1: comparability of study populations (age and clinical indication)

	N= NBCA + NBCA-MS (%)		N=NBCA(%)	N=NBCA-MS(%)	P=
Mean age (years) N=83			33.0	33.9	0.487
Clinical indication N= 112	impotention N=11 (9.8)		5 (45.4)	6 (54.6)	0.556
	inconvenience N=25 (22,3)	infertil N=3 (2.7)	2 (66.6)	1 (33.4)	
		no infertil N=22 (19.6)	9 (40.9)	13 (59.1)	
	preventive N=6 (5.4)		5 (83.3)	1 (16.7)	
	infertility N=70 (62.5)	primary N=67 (59.8)	32 (47.8)	35 (52.2)	
		secondary N=3 (2.7)	1 (33.4)	2 (66.6)	

Table 2: comparability of study populations (clinical classification)

	N= NBCA + NBCA-MS (%)		N=NBCA(%)	N=NBCA-MS(%)	P=
Clinical classification N=97*/112 (86.6%)	left N=84 (86.6%)	subclinical N=13 (13.4)	7 (53.8)	6 (46.2)	0.951
		grade 1 N=22 (22.7)	10 (45.4)	12 (54.5)	
		grade 2 N=27 (27.8)	12 (44.4)	15 (55.6)	
		grade 3 N=22 (22.7)	11 (50.0)	11 (50.0)	
	right N=13(13.4%)	subclinical N=5 (5.0)	2 (40.0)	3 (60.0)	0.644
		grade 1 N=7 (7.2)	2(28.6)	5 (71.4)	
		grade 2 N=1 (1.2)	0 (0.0)	1 (100.0)	
		grade 3 N=0 (0.0)	0 (0.0)	0 (0.0)	

* Clinical Classification according Dubin and Amelar

* 15 treated varicoceles were not diagnosed clinically and not classified before.

Table 3: comparability of study populations (phlebographic classification)

	N= NBCA + NBCA-MS (%)			N=NBCA(%)	N=NBCA-MS(%)	P=
Phlebographic classification	left:84 (75)	type 1 N=33 (39.2)		16 (48.5)	17 (51.5)	0.275
N=112		type 2 N=16 (19.0)	2a N=6	2 (33.3)	4 (66.7)	
			2b N=10	6 (60.0)	4 (40.0)	
		type 3 N=12 (14.3)		8 (66.6)	4 (33.4)	
		type 4 N=22 (26.2)	4a N=4	0 (0.0)	4 (100.0)	
			4b N=18	8 (44.4)	10 (55.6)	
		type5 N=1 (1.2)		0 (0.0)	1 (100.0)	
	right:28 (25)	type 1 N=2 (7.1)		1 (50.0)	1 (50.0)	0.604
		type 2 N=14 (50)	2 N=6	5 (83.3)	1 (16.7)	
			2a N=8	4 (50.0)	4 (50.0)	
		type3 N=1 (3.5)		0 (0.0)	1 (100.0)	
		type 4 N=11 (39.3)	4 N=3	1 (33.3)	2 (66.7)	
			4a N=8	3 (37.5)	5 (62.5)	

*Phlebographic classification according Bähren (left side) and Siegel (right side)

Table 4: Efficacy of both glues

	N= NBCA + NBCA-MS (%)		N=NBCA(%)	N=NBCA-MS(%)	P=
efficacy	N=111*/112		54/54 (100%)	55/57 (96,5%)	0.244
the embolization plan		fulfillment 3 of 4 steps	45/54 (83,3%)	41/58 (70,7%)	0.124
N= 112		fulfillment all 4 steps	25/54 (46,3%)	15/58 (25,9%)	0.030

*One patient had no control phlebography because of an acute allergic reaction with transport to the Intensive Care-unit.

Safety of the tissue adhesive

Stability of the embolus at the start of embolization was defined as the absence of sudden disruption of the glue embolus proximally or distally. Stability of the embolus 10 minutes after embolization was defined as unchanged location and configuration of the embolus.
A specific safety issue is sticking of the tissue adhesive to the microcatheter. Although gluing of the microcatheter is rare, glue droplets adhering to the catheter might cause disruption of the embolic cast (with possible recanalization), occlusion of the guiding catheter (precluding control venography) or inadvertent embolization into the renal (or caval) vein at time of microcatheter withdrawal. Sticking of glue to the microcatheter is more likely with reflux. Reflux was confirmed when the embolus did not remain distally from the catheter tip. Occlusion of the microcatheter was defined as no ability to flushing with glucose 10%, performed outside the patient. Technical and clinical complications during the procedure were noted.

Statistical analysis

Demographic, clinical and phlebographic characteristics of both patient groups were compared with the Mann-Whitney U-test and the Fisher's exact test. Efficacy and safety parameters for both products were assessed by the Fisher's exact test. A p-value of less than 0.05 was considered as significant different.

RESULTS

Comparability of both study populations

An equal number of left (N=40 and N=44) and right (N=14 and N=14) spermatic veins were treated with NBCA and NBCA-MS (P=0.831). We treated 80 insufficient left spermatic veins of which two in a 2-step planned embolization and two with repeat glue injection, hence counting for 84 left-sided embolizations. Age (P= 0.487), clinical indication (P=0.556) (table 1), clinical and phlebographic classification (table 2 and 3) of the left (P=0.951 and P=0.275 respectively) or the right (P=0.644 and P=0.604 respectively) varicocele did not differ between both groups.

Comparison of efficacy of both glues

No significant difference between the efficacy of the two NBCAs to occlude the spermatic vein and stop reflux was observed (P = 0.244; *(table 4)*). Occlusion was confirmed after one single embolization act with NBCA in all but one (N=53/54) and with NBCA-MS in 54 of 57 spermatic veins. In two cases, one of each glue group, a double spermatic vein compelled us to plan the embolization in a two-step act. All four veins were occluded by a single glue injection. Only in 2 planned single-step cases, all with NBCA-MS, contrast reflux to the plexus persisted on control phlebography. Small spermatic branches remaining patent (one case) and insufficient glue in one branch of a bifurcated internal spermatic vein (one cases) were responsible for restitution of flow to the pampiniform plexus, requiring a second embolization with the same agent. If we look at the accomplishment of step 3 of the embolization plan (filling with glue of all targeted side-branches and parallel veins), in 9/54 (16.6%) of NBCA and in 10/58 (17.2%) of NBCA-MS procedures, we

evaluated this step as unsatisfactory (like in the one with a patent bifurcated medial spermatic vein). Fulfillment of the embolization plan with accomplishment of at least 3 out of four steps, was not significant different between both groups (NBCA N=45/54, 83.3% versus NBCA-MS N=41/58, 70.7%; P = 0.124). If all 4 steps had to be respected, then the embolization plan was significantly less frequently fulfilled in the NBCA-MS group (P= 0.030). Comparing the steps separately, only step 4 (patency of the diagnostic catheter after embolization) revealed a significant difference in favor of NBCA (NBCA N=39/54, 72.2% versus NBCA-MS N=28/58, 48.3%; P= 0.012).

Safety of the glue

Both NBCAs showed the same stability at the start and at 10 minutes after embolization (P=0.083) and (P=1.000) respectively, although there was a trend towards higher initial stability of NBCA. At the beginning of the procedure, 24.1% (N=27/112) of the glue emboli were not stable and showed some degree of migration (NBCA N=9/54, 16.7% versus NBCA-MS N=18/58, 31.0%; P=0.083). After 10 minutes, all emboli remained unchanged compared to their initial form and location.
Sticking of embolic fragments to the microcatheter was equally frequently observed in the NBCA (N=25/54, 46.3%) as in the NBCA-MS group (N=29/58, 50.0%; P= 0.710).
Reflux of glue along the microcatheter, reflecting the inability to keep the glue distally from the microcatheter, was even frequently observed in both groups (NBCA N=37/54, 68.5% versus NBCA-MS N=44/58, 75.9%; P=0.406).
Reflux of glue (N=51/112) and stickability of glue to the microcatheter (N=81/112) were significantly associated in the whole population (P < 0.001) as well as within the group of veins treated with NBCA (P < 0.001) or with NBCA-MS (P < 0.001).
Only N=22/112 or 19.6% of the microcatheters were occluded after embolization. We have only a trend for more occlusions with NBCA (N=15/54, 27.8%) than with NBCA-MS (N=7/58, 12.1%; P=0.056). Obstruction of both guiding- and microcatheter was similar frequent for both products (NBCA N=4/54, 7.4% versus NBCA-MS N=4/58, 6.9%).
The only complication in our study was an acute allergic reaction immediately after embolization (in the NBCA-MS group) with hypotensive reaction, urticaria and permanent low blood pressure and finally transport to intensive care. After 3 h the situation was stabilized and 12 h later he could leave the hospital.

DISCUSSION

In this randomized and blinded study both tissue-adhesives (NBCA and NBCA-MS) were equally effective and safe for the embolization of varicoceles.

For clinical testing of NBCA-MS, we considered varicocele embolization an adequate model for several reasons. Spermatic vein anatomy is well defined, recognizable and to high extent homologous. As children were excluded and adults tend to have more complex spermatic vein anatomy, the embolization procedure was challenging. Flow in the spermatic vein is slow and reversed (away from the catheter tip), so that placement of a standardized and local embolus can be evaluated. The NBCA-embolus will tend to be in contact with the microcatheter so that adherence of the glue to it can be examined. Moreover, at our institution we have experience with NBCA in varicocele embolization in over 3000 patients.

The varicocele embolization model for NBCA testing is not new. In 2006, Heye et al. [30] published the results of a randomized study in 64 patients on the embolic effects of NBCA and NBCA-MS, finding both products equally efficient. However, in this study the radiologist was not blinded for the glue and the dose/dilution of the glues was different (1/0.8 versus glue/lipiodol). Moreover, the authors gave no details about handling and behavior of the glues during the different steps of embolization.

Heye et al. reported an occlusion rate of 100% with both glues, but we don't know how often they achieved this result in a single embolization act. In our series too, success rate for both NBCAs was finally 100% however, in 4 cases a second injection of glue was required to achieve success. Only anatomy was responsible for persisting of reflux and not blood flow along or through the placed glue embolus. In two of these cases, venous variants compelled us to change our embolization plan from the beginning to a two-step procedure. Only in two cases, both after a planned one-step NBCA-MS treatment, we had to repeat the embolization. At the cost of an extra microcatheter, additional NBCA-MS embolization leads to the desired occlusion.

As we assumed a high efficacy of glue, additional parameters in a so-called embolization plan would be needed to assess the handling of the two products. Fulfilling 3 of the 4 criteria of the embolization plan was not significantly different between NBCA and NBCA-MS (83.3 % respectively 70.7 %; P=0.124), although the absolute result for both glues was less well than we had initially expected. Obviously, there is a discrepancy between the efficacy of glue as an embolic agent and the necessity of completing a proposed embolization plan. Only the 4th parameter "the patency of the diagnostic catheter" was responsible for significance in favor of NBCA versus NBCA-MS (72.2% respectively 48.3%; P=0.012). Although, we knew of this problem by experience, we were surprised why occlusion so often happened with NBCA-MS. Of course, glue fragments adhering at the microcatheter can block the guiding catheter during withdrawal. However, sticking of glue to the microcatheter showed no differences between NBCA and NBCA-MS (46.3 % versus 50%; P=0.710). In experimental swine studies Levrier et al [25] found out that polymerization of NBCA-MS versus NBCA embolization was identical with regards to occlusion rate, but NBCA-MS casts were less adhesive to the vessel wall and could be pulled out with a residual thrombotic lining. In contrast, NBCA casts were strongly adhesive to the vessel wall and caused endothelium injury when removed. NBCA-MS glue fragments initially adhered to the microcatheter might have detached more easily during withdrawal, then clot together and obstruct the guiding catheter. But even this explanation is speculative since in our study, the adhesivity of both NBCAs to the microcatheter showed no significant difference, in contrast to the general opinion [31]. Occlusion of catheters after embolization was fortunately not determinative for occlusion of the varicocele.

Both NBCAs produced stable emboli and are therefore save for embolization of varicoceles. Between both NBCAs, we found no significant difference for stability at the start and at 10 minutes after embolization, although NBCA-MS tends to migrate distally more frequently at the start of the procedure. This tendency of NBCA-MS is attributed to its slower polymerization rate and lower vessel adhesivity, which are characteristics you also can take advantage of to push the glue distally, in case the distal endpoint should not be reached. Whether performed with NBCA or NBCA-MS, in half of the embolizations, glue fragments stuck to the microcatheter. Although we expected glue adherence, the incidence was high and, not surprisingly, firmly associated with reflux around the microcatheter overall and within the groups treated with NBCA and NBCA-MS (P<0.001). At the end of the embolization while reaching the proximal endpoint, it becomes difficult to keep the glue away from the microcatheter and accomplish all 4 steps of the embolization plan. However annoying glue sticking to the microcatheter is, it did not issue

consequences such as non-target embolization of the renal or caval vein.

During the study there was only 1 complication of an acute allergic reaction after embolization with NBCA-MS. To our knowledge there is no publication in literature about acute allergic reactions to cyanoacrylates after endovascular use. Nevertheless it seems that this severe allergic reaction was not due to the contrastagent because it started immediately after the embolization. Lipiodol is known as "ethiodised oil", containing poppy-seed oil, which could be the responsible for the allergic reaction. From this study, it seems that for the embolization of varicocele, the additional monomer MS offered no advantage. Moreover, a higher stability of the embolus and less stickability to the microcatheter could not be confirmed. With NBCA-MS more guiding catheters were occluded, although without influence on the final result of the embolization. Whether you should decide to use NBCA or NBCA-MS for venous embolization might depend on other factors as well. In Europe, NBCA has been widely used and is a low cost embolic agent, while NBCA-MS has the advantage of a CE-label and is as good as NBCA.

Although the efficacy of both glues is equally very high, we recognize that the power of the study to avoid a false negative conclusion (type II-error) is only 0.64. We should have enrolled 87 insufficient spermatic veins in each group to reach a level-beta of 0.80. Fulfillment of all 4 steps of the embolizationplan was significantly different and therefore doesn't seem to pose a power problem.

Moreover, the results of this study are based on glue embolizations performed by a radiologist highly experienced with tissue-adhesives and should not be indiscriminately generalized. In addition, glue used in non-experienced hands can be responsible for several risks of complications and relapses. In this study concept, we tested NBCA comparing it with NBCA-MS in the specific model of the internal spermatic vein. Whether the same conclusions can be drawn for embolization in other, particularly arterial, vessels should be the subject of further studies.

CONCLUSION

Both tissue-adhesives NBCA and NBCA-MS were equally efficient and safe for the embolization of varicoceles. The acclaimed improvement of the glue handling with NBCA-MS could not be substantiated.

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Tolerance of glue embolization under local anesthesia in varicoceles: A comparative study of two different cyanoacrylates

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ABSTRACT

Purpose: To find out whether in varicocele embolization the copolymer cyanoacrylate glue (NBCA-MS) has a better patient tolerance compared to the monomer n-butyl-2-cyanoacrylate (NBCA).
Materials and methods: $N = 112$ insufficient spermatic veins (left sided $N = 84$, right sided $N = 28$) diagnosed in $N = 83$ adult males were prospectively randomized for blinded embolization with either NBCA $N = 54$ (Histoacryl) or with NBCA-MS $N = 58$ (Glubran2). Before, during and up to one week after embolization, patient discomfort was assessed by a standardized pain scale. Type, location and side of discomfort were noted.

Statistical analysis was performed with the Mann–Whitney *U*-test, the McNemar test and the Fisher's exact test.

Results: Embolization caused discomfort in $N = 48/112$ (43%) spermatic veins, comprising $N = 26/54$ (48%) in the NBCA group and $N = 22/58$ (38%) in the NBCA-MS group. During the week after embolization, the overall number of discomfort reports rose to $N = 62/106$ (59%), with an increase to $N = 30/53$ (57%) in the NBCA group and to $N = 32/53$ (60%) in the NBCA-MS group. The number of immediate grade 2 to 4 pain reactions was $N = 22/112$ (20%), and rose to $N = 37/106$ (35%) after one week. No difference in discomfort during embolization and at 1 week after treatment was noted. Characteristics, severity grading, and location of discomfort were similar in both NBCA groups, regardless the time point of observation.
Conclusion: Discomfort after glue embolization of varicocele is a common side effect, which might evolve to pain. The assumed lower inflammatory reaction on NBCA-MS was not translated in an improved tolerance.

1. Introduction

A varicocele is an abnormally dilated cluster of veins in the pampiniform plexus, caused by reflux of blood through insufficient valves in the internal spermatic vein (ISV) [1]. The incidence is rare before the age of 10 years, rises to 15% in the adolescent population and increases up to 45% in infertile males [2,3]. Treatment is indicated to relieve local discomfort and to improve male fertility [4]. Percutaneous embolization has the advantage over surgery because it is an outpatient procedure under local anesthesia with a faster return to normal activities and a considerable lower cost [4]. Recurrence rates for both techniques vary between 1.6 and 13% [5–9]. Although many materials have been proposed and used for embolization of varicoceles, it remains unclear whether coil placement has a lower recurrence rate than for instance the injection of an sclerosing agent. The concept that the complex venous network found in many cases of spermatic vein insufficiency should be completely obliterated was the principal reason for the use of a tissue adhesive [10,11]. Kunnen et al. already reported in 1980 a high success rate with IBCA (isobutyl-2-cyanoacrylate, bucrylate, Ethicon) [10]. Later on IBCA was replaced by NBCA (n-butyl-2-cyanoacrylate or embucrilate; Histoacryl transparent, Braun, Tuttlingen, Germany) by reasons of possible carcinogenicity [12–14]. NBCA causes an acute and chronic inflammatory reaction expressed clinically in varicoceles by local pain and discomfort. The Food and Drug Administration (FDA) refused subsequently to approve NBCA for intravascular application, untill Trufill demonstrated recently its value for embolization of intracranial arterio-venous malformations [15]. In Europe, the company never applied for or received a CE-label for intravascular use.

For many years research was concentrated on extension of the carbon group of the NBCA, however it was only after introduction of the copolymer NBCA-MS (Glubran 2) that a glue component with a lower exothermic reaction and a higher stability became

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Preface to part 1.2

Experimentally, Glubran2 proved to have a lower toxicity resulting in a lower inflammatory reaction [(1)]. These findings could point at a better tolerance for the embolic agent during and after embolization.

In 2006, Heye already used the model of the varicocele to compare NBCA and NBCA-MS [(2)]. In addition to the technical success, the pain response during the embolization was evaluated by means of a Visual Analogue Scale (VAS). He reported a mean pain score of 3.25 on VAS and no significant difference between NBCA and NBCA-MS.

Our experience learns that glue causes mild to moderate pain during embolization in some of the patients. This fits with the above-mentioned mean pain score of 3.25 on VAS. But even 1 week after embolization, some patients complain about discomfort at the height of the abdominal flank without the presence of a thrombophlebitis of the PP. These findings are always associated with the localization of the glue, but seem to be unpredictable and patient dependent. For this reason, we assessed not only the pain during embolization but also evaluated the post-embolization inflammatory reaction.

Within the same double-blinded prospective randomized study, we registered the discomfort during, just after and during the first week after the embolization (aim 1&4).
The study included only adults, who should report pain less subjectively than children. Continuous recording of pain or discomfort during embolization is a more accurate representation of what the patient experiences. Therefore, we replaced the VAS scale by a numerical scale that was related with hand movements of the patient.
An advantage of this method is that the patient did not have to speak during the embolization, thus avoiding involuntary pressure changes. To record post-embolization pain during one week, a questionnaire was given to the patient, on which he could note the pain score, localization, duration and possible medication intake. Bilateral varicoceles which were deliberately treated with different glues, allowing us to compare the glues in one and the same patient.

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4. 1.2 Tolerance of glue embolization under local anesthesia in varicoceles: A comparative study of two different cyanoacrylates.

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ABSTRACT

PURPOSE:

To find out whether in varicocele embolization the copolymer cyanoacrylate glue (NBCA-MS) has a better patient tolerance compared to the monomer n-Butyl-2-Cyanoacrylate (NBCA).

MATERIALS AND METHODS:

N= 112 insufficient spermatic veins (left sided N= 84, right sided N= 28) diagnosed in N=83 adult males were prospectively randomized for blinded embolization with either NBCA N=54 (Histoacryl) or with NBCA-MS N=58 (Glubran2). Before, during and up to one week after embolization, patient discomfort was assessed by a standardized painscale. Type, location and side of discomfort were noted.

Statistical analysis was performed with the Mann-Whitney U-test, the McNemar test and the Fisher's exact test.

RESULTS:

Embolization caused discomfort in N=48/112 (43%) spermatic veins, comprising N=26/54 (48%) in the NBCA group and N=22/58 (38%) in the NBCA-MS group. During the week after embolization, the overall number of discomfort reports rose to N=62/106 (59%), with an increase to N=30/53 (57%) in the NBCA group and to N=32/53 (60%) in the NBCA-MS group. The number of immediate grade 2 to 4 pain reactions was N= 22/112 (20%), and rose to N=37/106 (35%) after one week. No difference in discomfort during embolization and at 1 week after treatment was noted. Characteristics, severity grading, and location of discomfort were similar in both NBCA groups, regardless the time point of observation.

CONCLUSION:

Discomfort after glue embolization of varicocele is a common side effect, which might evolve to pain. The assumed lower inflammatory reaction on NBCA-MS was not translated in an improved

tolerance.

INTRODUCTION

A varicocele is an abnormally dilated cluster of veins in the pampiniform plexus, caused by reflux of blood through insufficient valves in the internal spermatic vein (ISV) [1]. The incidence is rare before the age of 10 years, rises to 15% in the adolescent population and increases up to 45% in infertile males [2, 3]. Treatment is indicated to relieve local discomfort and to improve male fertility [4]. Percutaneous embolization has the advantage over surgery because it is an outpatient procedure under local anesthesia with a faster return to normal activities and considerable lower cost [4]. Recurrence rates for both techniques vary between 1.6 and 13 % [5-9]. Although many materials have been proposed and used for embolization of varicoceles, it remains unclear whether coil placement has a lower recurrence rate than for instance the injection of a sclerosing agent. The concept that the complex venous network found in many cases of spermatic vein insufficiency should be completely obliterated was the principal reason for the use of a tissue adhesive [10, 11]. Kunnen et al already reported in 1980 a high success rate with IBCA (Isobutyl-2-Cyanoacrylate, Bucrylate, Ethicon) [10]. Later on IBCA was replaced by NBCA (n-Butyl-2-Cyanoacrylate or Embucrilate; Histoacryl transparent, Braun, Tuttlingen, Germany) by reasons of possible carcinogenicity [12, 14]. NBCA causes an acute and chronic inflammatory reaction expressed clinically in varicoceles by local pain and discomfort. The Food and Drug Administration (FDA) refused subsequently to approve NBCA for intravascular application, until Trufill demonstrated recently its value for embolization of intracranial arterio-venous malformations [15]. In Europe, the company never applied for or received a CE-label for intravascular use.

For many years research was concentrated on extension of the carbon group of the NBCA, however it was only after introduction of the copolymer NBCA-MS (Glubran 2) that a glue component with a lower exothermic reaction and a higher stability became commercially available. The company General Enterprise Marketing (Viareggio, Lucca, Italy) received a CE label for intravascular use after animal studies demonstrating a lower histotoxicity and inflammatory reaction [16-18]. According to the manufacturer, NBCA-MS should have the same embolic capacities as NBCA, which was confirmed by two randomized controlled trials [11, 19].

Concerning the side effects of NBCA-MS the issue is less clear. Heye et al. did not reveal any difference between NBCA and NBCA-MS , but their study had several shortcomings [19]. In Heye's study, the investigator was not blinded for the glue. Pain sensation was only evaluated at the end of the procedure, while continuous registration during the procedure might be more accurate. Heye et al. investigated only the acute pain reaction and not the post inflammatory pain during the week after embolization. They included also children in the trial, who might be less reliable in reporting pain sensation. Therefore we initiated a blinded comparative prospective randomized study with the varicocele as a model to find out whether NBCA with the co-monomer (MS) is clinically better tolerated than the classical NBCA.

MATERIALS AND METHODS

Patient's selection criteria

We prospectively randomized 112 spermatic veins in 83 adult patients to be treated either by NBCA or by NBCA-MS. In the same patient, the left varicocele could be randomized to a different embolic agent than the right one. A similar number of left (N=40 and N=44) and right (N=14 and N=14) spermatic veins were treated with either NBCA or NBCA-MS.

Reasons for treatment consisted of impotence, clinical inconvenience with or without infertility, primary or secondary infertility and prophylactic embolization. The study was approved by the ethical board of our hospital. All participating patients signed the informed consent to participate the study (ethical board number 2003/081).

Technical aspects

Phlebographies of the renal vein and the ISV were performed using 6 French (F) diagnostic catheters (Cook Europe, Bjaeverskov, Denmark) after local anaesthesia with Lidocaine 1% (Xylocaine NV Astra Zeneca, Brussels, Belgium). Technical aspects of embolization with glue were described extensively elsewhere [11, 19].The 3 F Microferret microcatheter (modified coaxial infusion set with slip-coat hydrophilic coating) (Cook Europe, Bjaeverskov,Denmark) was then positioned supra-inguinal or as low as possible to perform a superselective distal venography in supine position.

The injection of glue was started from above the inguinal region. The cyano-acrylate was delivered during slow withdrawal of the microcatheter up to the level of the renal vein. We aimed at occluding the spermatic vein along with parallel veins or all relevant side-branches or renospermatic bypasses. The embolization was performed as an outpatient procedure.

Randomization and blinded set-up

Randomization was done by a computer random generator producing a continuous list of "0 "(NBCA) and "1" (NBCA-MS) numbers. Each insufficient spermatic vein was connected to one number on the list and was embolized with the allocated glue. The interventional radiologist and the patient were blinded for the type of glue used. A technical assistant prepared the glue in a separate room. In a 3 ml syringe, either 1 cc of NBCA or 1 cc NBCA-MS was mixed with 1.2 cc or 1.0 cc of Lipiodol Ultra-fluide (Liopidol Ultra-fluide, Laboratoire Guerbet, Roissy, France) respectively. The decision to utilize a mixture with a higher concentration of NBCA-MS was empirical based on the supposed slower polymerization rate of Glubran2 [18]. The blinded operator received the 3 cc syringe always filled with 1.8 cc of the allocated glue mixture. As both glues have the same odor and color, it was not possible for the operator to guess which one he was using. All embolizations in the study were done by the same experienced operator well acquainted with tissue adhesives.

Table 1: adapted pain scale

	left hand movements	pain scale	Visual Analoge Scale
0	does nothing	patient feels nothing	0
1	shows 1 finger	patient feels something but has no pain	1-3
2	shows 2 fingers	patient has pain but bearable	4-6
3	shows 1 hand	patient has a clear pain	7-8
4	shows 1 moving hand	patient has a severe and unbearable pain	9-10

Patient's comfort and side-effects during and after embolization.

Discomfort and the degree of discomfort are subjective parameters, which might differ between patients. Patients with a lower pain threshold will indicate discomfort more rapidly. Comparing measurements with the same painscale can make these parameters more objective, easier to assess and it has the advantage to detect the most painful period of the procedure. During the procedure patients can suffer or they can feel nothing and this can be indicated as discomfort "yes" or as discomfort "now". As an additional evaluation, patients were instructed to score on a pain scale (table 1) from 0 to 4, where 0 means " feel nothing" and 4 is associated with severe pain. No sedatives or pain medication were administered before embolization.

Pain reference test during local anesthesia

Local anesthesia was performed with 8 cc Xylocaine 1% (NV Astra Zeneca, Brussels, Belgium) through a 21 G intramuscular needle (BD Medical Systems, Drogheda, Ireland) and standardized by the same operator in all procedures. We know that local anesthesia caused some discomfort and by analyzing this discomfort on the same pain scale we could detect low pain threshold patients.

Discomfort during and after embolization

"During embolization" is defined as the period between the start of glue injection until the withdrawal of the microcatheter. Patients were instructed to score pain by standardized hand movements based on a visual analogue scale score (VAS) as shown in table 1. The use of a classical VAS score during the embolization was not workable. The highest score during the procedure was taken into account as well as the characteristics of the pain (immediately or later). "After embolization" means the period between the end of the procedure and the moment the patient left the hospital. Intake of analgesic or non-steroid anti-inflammatory drugs (NSAID) was noted.

Discomfort during 1 week after embolization

This evaluation was done by completing a questionnaire at home where patients could indicate persisting or late onset discomfort. Patients were asked to localize the discomfort on a drawing, presenting the groin, the testicles, the scrotum, the penis and the hypochondrium. Other inconveniences, duration of pain (hours or days) or the intake of drugs could be written on the questionnaire.

Sample size calculation and statistical analysis

Parameters concerning discomfort were analyzed by a combination of the Fisher's exact test, the McNemar test and the Wilcoxon matched-pairs signed-ranks test. A P-value of less than 0.05 was considered as significantly different. Given the assumed qualities and properties of the new adhesive we calculated the power of this study to detect at least a 30% difference in discomfort between the new and the old NBCA. Power analysis calculated 39 spermatic vein embolization per treatment arm (78 in total) to demonstrate a difference between the two NBCA's with a 80% power and alpha = 0.05. We performed an additional 34 spermatic veins to have at least 50 in each group [20].

Table 2: degree of discomfort during, immediately after and at one week after embolization

N= discomfort reporting /all embolized veins	degree	NBCA N=(%)	NBCA-MS N=(%)	P=
during embolization	0	28/54(52)	36/58(62)	
	1	15/54(28)	11/58(19)	
	2	7/54(13)	10/58(17)	
	3	3/54(6)	1/58(2)	
	4	1/54(2)	0/58(0)	0.408
after embolization	0	33/54(61)	39/58(67)	
	1	14/54(26)	13/58(23)	
	2	6/54(12)	6/58(10)	
	4	1/54(2)	0/58(0)	0.842
1 week after embolization	0	23/53(43)*	21/53(40)*	
	1	12/53(23)	13/53(24)	
	2	18/53(34)	18/53(34)	
	3	0/53(0)	1/53(2)	0.968

Note * In N= 6 patients (12 embolized spermatic veins) no questionnaire was returned.

RESULTS

Discomfort during local anesthesia

In 63% (N=71/112) of the embolized spermatic veins, patients mentioned discomfort during local anaesthesia. Most patients (N=68/71, 96%) felt something but had no pain (grade 1).

Discomfort during and after embolization (table 2)

In 43% (N=48/112) of the spermatic vein embolizations patients reported discomfort (grade 1 or more) during embolization, which was only in 20% (N=22/112) painful (grade 2 or more). None of the patients required medication during embolization. Both NBCA's caused discomfort in an equally number of patients: N=26/54(48%) for NBCA and in N=22/58(38%) for NBCA-MS, (P=0.340). The degree of discomfort was similar for both NBCA's (P=0.408) (table 2). Significantly more patients reported discomfort during local anesthesia than during embolization (P=0.002). The onset of discomfort was similar for both groups (P= 1). In 31% (N=15/48) there was an acute start of the discomfort (N=8/48, 17% for NBCA and N=7/48, 15% for NBCA-MS) and in 69% (N=33/48) the discomfort occurred progressively (N=18/48, 69% for NBCA and N=15/48, 68% for NBCA-MS).

In 36% (N=40/112) of the treated spermatic veins, patients continued to report discomfort after embolization (grade 1 or more). In only 12% (N=13/112) pain was reported (grade 2 or more). Discomfort was noted in N=21/54, 39% for NBCA and in N=19/58, 33% for NBCA-MS. There was no difference in reported discomfort (P=0.557) or reported degree of discomfort (P=0.842) between both glues (table 2).

Discomfort during one week after embolization

In N=77 patients (N=106 embolized veins), information about discomfort in the post embolization week could be obtained. Six patients did not return the questionnaire. The questionnaire revealed discomfort in N=30/53, 57% for NBCA and in N=32/53, 60% for NBCA-MS. The one-week discomfort and discomfort grading was not significantly different between both NBCA groups (P=0.844 respectively P=0.968) (table 2). When compared to the glue tolerance at embolization, we noticed a significantly higher number of discomfort reporting during the week after embolization (N=44/106, 42% versus N=62/106, 58%; P= 0.011). Prolonged or recurrent pain sensations (grade $\geq$ 2) were more often observed after embolization than pain during embolization (N=37/62, 59% versus N=20/44, 45%).

Drug intake was similar for both glues (N=9/19(47%) for NBCA an N=10/19(53%) for NBCA-MS; P=1.0). In N=19/62 (31%) cases with late discomfort we prescribed a non-steroid anti-inflammatory drug. Neither localization (P=0.722) nor side of discomfort (P=0.582) was significantly different between the two NBCA's (table 3). Eighteen patients underwent bilateral embolization with a different NBCA for each side (table 4). The number of patients that reported complaints at the side embolized with NBCA was higher than the number complaining of discomfort at the NBCA-MS side (N=9/18(50%) versus N= 5/18(28%). This trend was reversed at one week after embolization, when more discomfort was present at the NBCA-MS side N= 9/18(50%) versus (N=8/18(44%).

Table 3: drug intake, localization and side of discomfort at one week after embolization in complaining patients (N=62)

N= number of embolizations / total number of embolizations (%)		NBCA N=30(%)	NBCA-MS N=32(%)	P=
Localization of discomfort	Hypochondrium	12(40)	13(41)	
	Inguinal	10(33)	13(41)	
	Testicle and combinations	8(27)	6(19)	0.722
side of discomfort	right side	5(17)	8(25)	
	left side	21(70)	18(56)	
	bilateral	4(13)	6(19)	0.582

However paired comparison of the two NBCA's in the same patient revealed no significant difference for pain and grading of pain during embolization (P=0.219 and P=0.124 respectively), just after embolization (P=0.375 and P=0.279 respectively) and 1 week after embolization (P=1.0 and P=0.785 respectively). A similar observation could be done when looking at the whole study group, but the difference there between the two NBCA's is less pronounced and also not significant (table 2). Medication intake in this subgroup was not different (P=0.500) (table 4).

Table 4: discomfort in 18 patients embolized bilaterally (left side with NBCA and right side with NBCA-MS, or vice versa)

number of patients N=18 (embolized veins N= 36)			NBCA N= (%)	NBCA-MS N= (%)	P=
during embolization	discomfort	yes	9(50)	5(28)	0.219
	grade of discomfort	1	6(33)	2(11)	
		2	2(11)	3(17)	
		4	1(6)	0(0)	0.124
After embolization	discomfort	yes	7(39)	4(22)	0.375
	grade of discomfort	1	5(28)	1(6)	
		2	1(6)	3(17)	
		4	1(6)	0(0)	0.279
1 week after embolization	discomfort	yes	8(44)	9(50)	1.000
	grade of discomfort	1	4(22)	5(28)	
		2	4(22)	4(22)	0.785
Medication at one week			2(11)	4(22)	0.500

DISCUSSION

This prospective randomized and blinded trial could not substantiate the potential advantage of the newer NBCA-MS in reducing pain and discomfort during embolization. Patient's discomfort during varicocele embolization, whether done with NBCA or NBCA-MS, was similar (P= 0.340), so was discomfort immediately after treatment (P= 0.557) and during the week post embolization (P= 0.844). Moreover, the discomfort (score 1 - 4) or pain severity (score 2 or more) complained during embolization (P= 0.408), immediately after (P= 0.842) and during one week after (P= 0.968) treatment did not differ between both glues. These findings are in contrast to the widespread opinion that NBCA-MS would be safer and painless. In a recent review article on varicocele embolization, advice was given to use NBCA-MS instead of NBCA for this proper reason [21]. Why NBCA-MS is generally supposed to be superior remains unexplainable since Heye et al. already pointed out that it is probably not.

Although both glues are equally effective agents in varicocele embolization and probably, but not specifically tested, for embolization in other indications, it should be clear that a number of patients will suffer local pain or discomfort [11, 19]. Pain is caused by the exothermic heat, which is produced by the polymeralization and the subsequent inflammatory reaction. The exothermic heat reaction is apparently not modulated by the methacryloxysulfolane copolymer added to the cyanoacrylate in Glubran2.

In about one of five (18%) embolized veins, patients will complain of pain, a number that could be biased by abnormal pain thresholds. By choosing pain discomfort under local anesthesia as a pain reference test, we could ascertain that the patients in our series had a normal pain sensitivity (37% had no discomfort during anesthesia and of the others, 96% had a score 1 discomfort). Varicocele embolization is an adequate model for discomfort testing, because it consists of a homogeneous group of young and healthy adult males. Moreover, as we performed the procedures under local anesthesia, the signs of discomfort or pain could be coincident with the appearance of the glue in the vein and objectified by allocating the pain to the level where the glue exited the microcatheter.

Proving that the post-embolization discomfort was a late inflammatory reaction to the glue is less evident. We know that at one week, the number of patients complaining was significantly higher than at embolization, consistently in both groups of NBCA. In both groups, patients localized concordantly the discomfort region where the glue embolus was usually set (mostly at the hypochondrium or the inguinal region) and correctly allocated the side of embolization (right, left). Although these observations sustain a causal relationship between discomfort and NBCA, it remains remarkable that a high number of patients (>50%) had discomfort at one week, but did not complain during embolization. Vice versa, one of three patients having pain during embolization, was free of symptoms at one week. Thus, symptoms at one week are to be ascribed to a different, subacute inflammatory reaction most probably to NBCA degradation products, which seems patient-dependent and controllable by NSAID. A prophylactic analgesic treatment with NSAID post embolization could be considered but should be weighed against the fact that almost half of the patients will not need it.

The varicocele embolization model for NBCA testing is not new. Heye et al. revealed that there was no evidence of a different pain sensation during embolization with NBCA-MS in comparison with NBCA [19]. However, in this study, the investigator was not blinded for the glue and pain sensation was only evaluated at the end of the procedure by a VAS questionnaire. We believe that

continuous registration of discomfort during the procedure reflects more precisely what the patient feels. For that reason, we modified the VAS in a paper with fixed numeric scores related with hand movements. Heye et al. included children in the trial and pointed at an even unexpected trend that NBCA could be less painful in the young patient and more painful in the older patient than NBCA-MS. As in our study only adult patients were included, our data can not shed light on this matter.

Because concomitant right spermatic vein insufficiency was treated with the concurrent NBCA, we had a small subgroup of 18 patients for checking intra-patient consistency of pain reporting. We conclude from this subgroup that the pain is consistent, side independent and that the two NBCA's are not significant different for a paired comparison. However, we detected a trend in more complaints regarding the side embolized with NBCA than from the NBCA-MS side (50% versus 28%). This trend was reversed at one week after embolization, when more discomfort existed at the NBCA-MS side (50% versus 44%). A similar but less pronounced observation could be seen for the whole study group. It might be that the comparison of both glues is more realistic when used in the same patient. Subsequently, the difference of 22% in acute reactions, could become significant if we had a larger subgroup of patients with bilateral varicoceles. This study included 112 spermatic vein embolizations, a number which should be large enough to demonstrate a clinical significant difference in discomfort. The assumed reduction of thirty percent in the number of patients complaining of discomfort with the modified glue was clearly not achieved. Smaller changes would be clinically less relevant in our opinion, even if recruitment of more patients could increase the power of the study (at least 186 for a 20% difference). If you have to determine whether to use NBCA or NBCA-MS for venous embolization of varicoceles or for other indications but under local anaesthesia, then your decision should probably not be based on efficacy, handling, safety or tolerance of the NBCAs [11, 19]. Choice of NBCA will be determined by availability, costs and more specific by FDA indication approval or the existence of a CE-label for intravascular use (European Union).

CONCLUSION

Both tissue-adhesives "NBCA" and "NBCA-MS" caused a similar mild degree of discomfort during embolization of varicoceles. NBCA-MS is of no benefit to NBCA for pain sensation or late inflammatory discomfort. The discomfort is self-limiting and did not hinder the completion of the procedure.

CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

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Preface to part 1.3

Embolization with glue, as described in the previous 2 parts is an efficient and safe method to treat varicoceles. We demonstrated that the endovascular injection of glue might cause a discomfort and a mild pain during embolization and in the week after it. Although glue injection is very efficient to occlude the ISV and probably relevant collaterals, we detected that in complex ISV anatomy even glue could not penetrated as deep as we wished.

Onyx (ethylene-vinyl alcohol) is a plastic dissolved in dimethyl sulfoxide (DMSO). Onyx solidifies after diffusion of the DMSA to a solid cast, which can be pushed and extended in different directions in the vessel. For the embolizations of cerebral arterio-venous malformations (c-AVM) and dural fistulas (d-AVF) we have replaced glue by Onyx since many years in our department. Onyx proved its superiority to glue because it is less adhesive to the vessel wall and can penetrate much better and further through the feeders into the nidus of the c-AVM or into the complex network of the d–AVF. The embolization can be done slowly and controllable while performing control angiographies. Moreover, histology obtained from resected embolized AVM's, showed no inflammatory reaction in and around the vessel in contrast to resected glue-embolized AVM's.

Due to these characteristics, we thought that in varicoceles with complex anatomy and extensive collaterals, Onyx could better fill out and occlude the venous network. In order to increase the tolerability and efficacy of varicocele embolization, we started a pilot study (aim 1&5).

10 patients with a varicocele were embolized with Onyx, while investigating the feasibility, safety and comfort. We injected Onyx with the same technique as we used for glue. If reflux became more than 3 cm, we withdraw the microcatheter proximal to the reflux and continue the embolization. No more than 3 cc Onyx was injected to occlude the ISV. Discomfort and pain reaction during embolization and in one week after embolization were registered with the same numeric pain scale and questionnaire as we used in the previous glue study.

4. 1.3 Varicocele embolization with Onyx: a feasibility study

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ABSTRACT

RATIONALE AND OBJECTIVES

Our aim was to investigate the feasibility of ethylene-vinyl alcohol (Onyx) embolization for treatment of varicoceles and to determine patient's safety and comfort.

METHODS AND MATERIALS

Ten adult males with insufficient left spermatic veins were embolized with a maximum of 3cc Onyx. Technical success was defined as absence of contrast reflux to the pampiniform plexus on control phlebography. Technical success was complete if occlusion of the insufficient internal spermatic vein was achieved by one single Onyx injection.

Safety was assessed by the occurrence of complications as well as by the patient's radiation dose. A pain scale was used to evaluate the patient's discomfort.

RESULTS

Technical success was achieved in 9/10 of the patients. In one patient, the predetermined amount of Onyx (3cc) was not sufficient. Complete technical success was achieved in 6 of 9 patients, as 3 patients required a second microcatheterization and Onyx injection. All patients experienced moderate to severe discomfort, which interfered with the embolization act. The mean radiation exposure was 3603.5 cGy/cm2 (range 1270.6-6867.0). No technical complications occurred.

CONCLUSION

Although embolization of varicoceles with Onyx is feasible, technical problems, combined with significant patient discomfort and a high radiation dose preclude at the moment its clinical use.

KEYWORDS: varicocele - embolization - ethylene-vinyl alcohol

INTRODUCTION

Varicoceles are abnormally dilated veins in the pampiniform plexus, found in about 15% of male adolescent and in 45% of males referred for infertility [1]. Surgical ligation as well as percutaneous embolization aims at blocking the blood reflux in the internal spermatic vein (ISV). Percutaneous embolization is an outpatient procedure performed under local anesthesia at a low cost and enabling fast return to normal activities [2]. Complication rate is lower than after open surgical or laparoscopic repair [3]. Recurrence rates after surgical ligation or percutaneous embolization vary widely from 1.6 up to 13 % according the technique used [4-8]. Embolization uses different materials such as stainless steel or platinum coils, detachable balloons, sclerosing agents and tissue adhesives [9-14]. Recurrence of varicoceles might either be caused by recanalization of the ISV due to deflation of the balloons, flow restoration through the delivered coils, or by insufficient blocking of collaterals that might maintain the reflux [10, 11, 13]. Liquid embolics were introduced to increase the destructive impact on the vessel wall over a larger area. Using flow dynamics during embolization, liquids can be pushed into collaterals and side-branches. However, the injection of non-radiopaque sclerosing agents is more or less blind and therefore the extent of the embolization is less predictable. It can take up to 30 min. before the impact of the agent on the venous wall becomes visible. By mixing Cyano-acrylate with Lipiodol Ultra-fluide, (Laboratoire Guerbet, Roissy, France), glue becomes a radiopaque liquid which is real-time visible during embolization. The penetration of glue in side-branches that might maintain the reflux depends on the polymerization rate and therefore this technique is not always controllable.

Onyx (ev3, Irvine, California, USA) is a biocompatible ethylene-vinyl alcohol copolymer (48 mol/l ethylene and 52 mol/l vinyl alcohol) (EVOH) dissolved in dimethyl sulfoxide (DMSO). Micronized tantalum powder is suspended in the liquid copolymer DMSO mixture to provide fluoroscopic visualization. In contact with blood DMSO diffuses from the mixture, causing a precipitation and solidification of the copolymer. The solidification of Onyx takes about 10 minutes, which allows longer injection times and subsequently a more controllable and effective vessel filling [15]. For this reason, Onyx was introduced for the embolization of arteriovenous malformations (bAVM's) and dural fistulas (dAVF) of the brain, and proved to be superior to tissue-adhesives [15-18]. For each microcatheterization and Onyx injection, a larger part of the bAVM nidus could be filled and excluded. Even more fascinating is the capability of Onyx to penetrate in side-branches and to occlude a complex network of dural fistula feeders when injected from one single point [19]. In analogy, we thought that the venous network of paraspermatic and renospermatic collaterals that is usually linked with the insufficient ISV, could be more effectively blocked with Onyx. The complete exclusion of the venous network would reduce the number of recurrences. There are clinical reports on the use of Onyx in bleedings and endoleaks, but only few that illuminate its role in treatment of peripheral AVMs and none on the use in the venous system [20-23]. In an experimental animal study, Onyx showed the capacity of penetrating from a wedged hepatic vein position through the liver sinusoids into the portal vein, resulting in a controllable portal vein occlusion [24]. Onyx comes in different concentrations ranging from Onyx 18 (6% EVOH-94% DMSO), Onyx 20 (6.5% EVOH-93.5% DMSO) to Onyx 34 (8% EVOH-92% DMSO. In a pilot study, we intended to treat varicoceles in adult males with Onyx 20 (6.5% EVOH-93.5% DMSO). Additionally, as Onyx may induce pain and it will be injected under local anesthesia we wanted to evaluate patient's reaction and discomfort [20, 25].

MATERIAL AND METHODS

Patient selection

From December 2008 until August 2010, 87 adult patients were treated for varicocele. Because of other ongoing studies only 44 patients were left to be screened of whom finally 10 patients (age between 22 and 41 years / mean 30.7) gave informed consent to participate in the study. Exclusion criteria were age younger than 18 years, inability to understand the informed consent and previous varicocele treatment. 8 patients were treated for infertility and 2 for local discomfort. The operator (PV) was well acquainted with liquid embolization of the spermatic vein. The study was approved by the ethics committee of the hospital (EC: 2007/347).

Diagnostic phlebography of the ISV.

After local anesthesia with 10 cc Lidocaine 2% (Xylocaine NV Astra Zeneca, Brussels, Belgium) using a 21 G intramuscular needle (BD Medical Systems, Drogheda, Ireland), selective venographies of the renal veins and the internal spermatic veins were performed using a 6 French (F) femoral sheath and 6 F guiding catheter (Cobra-shaped and a Simmons-1 catheter respectively for the left and the right ISV) (Cook Europe, Bjaeverskov, Denmark). The phlebography was done in reverse Trendelenburg position on an Iconos R 200 tilt table with semi-automatic pulsed fluoroscopy (Siemens, Erlangen, Germany) under Valsalva manoeuvre with a non-ionic isotonic contrast-agent (Iodixanol 270 mgI/ml, GE Healthcare, Wemmel, Belgium). Venous insufficiency was substantiated by spontaneous retrograde opacification of the ISV and the pampiniform plexus, corresponding to the Bähren classification (types 1, 2a, 3, 4a and 5) [(26)]. Below competent valves (Bähren types 2b and 4b), reversed flow in the ISV is caused by reflux from collaterals. Proximal competent valves were usually crossed with the 6F catheter, distal valves with a 2.8 F Rebar TM 0.027 microcatheter (ev3, Irvine, Calif) during coughing or Valsalva manoeuvre. Paraspermatic veins, collaterals to the lumbar venous plexus or renospermatic bypasses to the ISV were mapped by contrast injection through the microcatheter with the patient in a supine position.

Embolization technique with Onyx

The microcatheter, positioned just proximal of the inguinal ring, was preloaded with 0.35 ml DMSO to fill the microcatheter's "dead space" and to prevent early Onyx precipitation. For this pilot study we choose the middle concentration of EVOH (Onyx 20). Onyx was aspirated into a 1 ml syringe and 0.35 ml was injected slowly for 60 sec to replace the DMSO from the catheter's "dead space". Once appearing in the vein, Onyx was injected slowly (0.1cc/min) under fluoroscopy to prevent early reflux and vasospasm. When reflux was observed, the injection was stopped for at least 1 minute and then resumed. Embolization was continued until a dense filling of the main vein with Onyx was achieved. In this feasibility study, our approach with Onyx was based on techniques and precautions described for the use of tissue-adhesives in spermatic vein embolization [(14)]. Therefore, we tolerated Onyx reflux up to 3 cm and then we pulled the microcatheter back just proximal to the reflux and we continued the embolization. Once we assumed that the Onyx embolus blocked the ISV over at least 3 cm completely and we could observe Onyx in the previously recognized collaterals, we stopped the injection and withdrew the microcatheter.

Table 1: Adapted pain scale

	left hand movements	pain scale
0	does nothing	patient feels nothing
1	shows 1 finger	patient feels something but has no pain
2	shows 2 fingers	patient has pain but bearable
3	shows 1 hand	patient has a clear pain
4	shows 1 moving hand	patient has a severe and unbearable pain

The procedure was considered technically successful when a control phlebography, in a tilted table position and using Valsalva manoeuvre confirmed the absence of reflux in the ISV (no appearance of contrast in veins of the pampiniform plexus). Patency of the guiding catheter was verified (absence of Onyx). If contrast medium appeared at the pampiniform plexus on control phlebography, then a new microcatheter was introduced to finish the embolization with additional Onyx proximal or adjacent to the previous Onyx cast. In glue embolization of varicoceles, we seldom used more than 3 cc to be successful. Therefore and for cost-effectiveness reasons, we limited the amount of Onyx to a maximum of two vials (3 ml). All patients received a lead shield around the scrotum. Patient's radiation dose was noted. If patients had a bilateral varicocele, then the right side was embolized with glue (Glubran2 or n-butyl-2-cyanoacrylate + Methacryloxysulfolane, NBCA-MS, General Enterprise Marketing, Viareggio, Lucca, Italy). In this way, we could compare local discomfort between glue and Onyx in the same patient.

Efficacy of Onyx

Technical success was defined as the absence of reflux of contrast medium to the pampiniform plexus after embolization with Onyx. We considered the technical success as complete if the occlusion could be achieved with one single catheterization and with the allowed amount of 3 cc Onyx. The mean Onyx injection time and the mean amount of Onyx injected were noted.

Safety of Onyx

Safety concerns were instability of the Onyx embolus, sticking of Onyx to the microcatheter during withdrawal, gluing of the microcatheter in the Onyx and radiation burden during the procedure.

First, inadvertent migration of Onyx proximally or distally in the ISV was checked during injection. Then, late alterations in location or configuration of the embolus, including pulmonary migration, were excluded at 10 minutes after finishing the injection. The total fluoroscopy time and the Dose Area Product (DAP) were registered for each patient.

Side effects of embolization with Onyx

We learned patients to score discomfort by hand movements during embolization, using an adapted visual analog pain scale from 0 to 4, where 0 meant " feel nothing" and 4 was associated with severe pain (table 1).

Pain reference test during local anesthesia

Discomfort and pain are subjective matters. Patients with a lower pain threshold will indicate discomfort more rapidly. By analyzing the discomfort during local anesthesia on the same pain scale, we aimed at detecting patients with a low pain threshold.

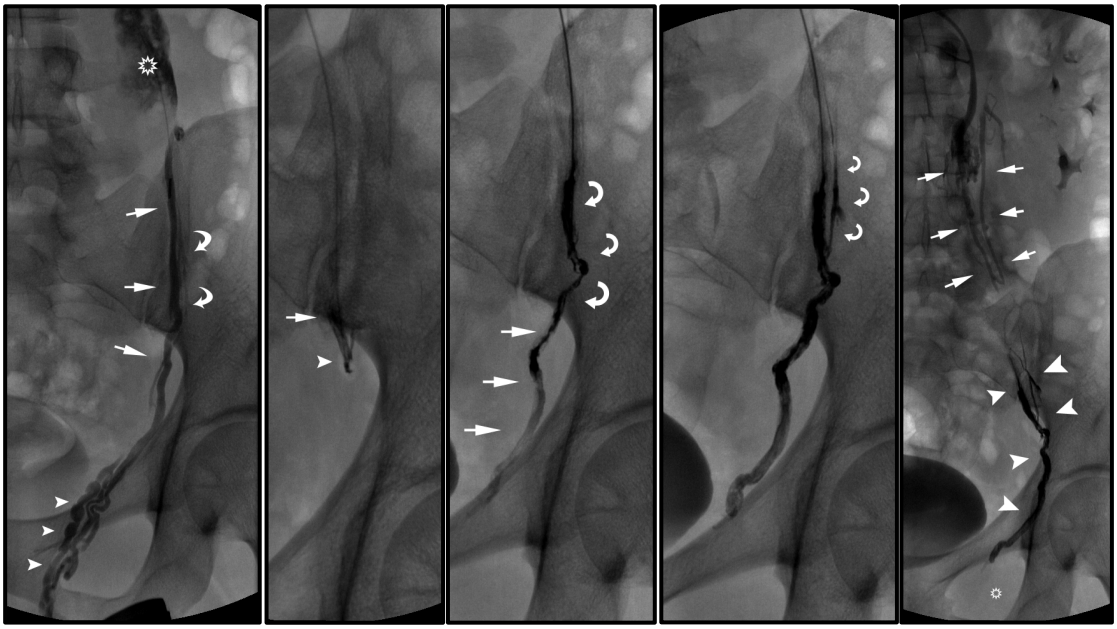
Discomfort during and after embolization

Discomfort was registered from the start of the embolization up to the withdrawal of the microcatheter to identify the local irritation caused by DMSO and Onyx. Only the highest pain score during embolization was validated.

We analyzed the way hand scores changed during embolization to define the pain character. For instance, a sudden change from score 0 to 3 reflected acute pain where a progressive change was rather stipulated as a chronic pain sensation. During post procedure observation and finally at discharge we interviewed the patient for his discomfort. Necessity of analgesic drugs was noted. No prophylactic sedatives or pain medication were administered.

By completing a comfort questionnaire at home at one week, patients could indicate late discomfort and specify its location on a drawing. Duration of pain (hours or days), the intake of drugs or other unspecified inconveniences, could be written on the questionnaire.

Fig 1: Case (pt 10) demonstrating complete technical success.
Fig1a : Microcatheter venography in a Bähren type 4b ISV insufficiency. After passing the competent valve, an insufficient ISV (arrows) with a small paraspermatic collateral (curved arrows) was revealed.Visualization of the pampiniform plexus (arrowheads).
Fig1b : Start of the Onyx embolization. Position of the tip of the Rebar microcatheter in the ISV (arrowhead) and early reflux of Onyx around the microcatheter (arrow).
Fig1c : Onyx cast with distal migration of the Onyx (arrows) and reflux of Onyx around the microcatheter (curved arrows)
Fig1d : During embolization, retrograde filling of the small paraspermatic collateral with Onyx (curved arrows).
Fig1e : Selective control venography (table tilt 45°) of successfully occluded ISV, demonstrating contrast agent in the cranial ISV and side-branches (arrows) and the Onyx embolus (arrowheads) in the caudal segment. Success was acclaimed by the absence of contrast reflux into pampiniform plexus (star).



RESULTS

Phlebographic classification

Six of 10 patients had incompetent proximal valves, exhibiting a single gonadal vein in 2 cases (Bähren type 1), a single vein with side-branches in 3 cases (Bähren type 2a) and a distal duplication in 1 case (Bähren type 3). Four patients showed veins with competent proximal valves and distal bypasses: one with connection to the lumbar plexus (Bähren type 2b) and three to renal collateral channels (Bähren type 4b). Thus 8/10 patients had an anatomically complex multichannel ISV insufficiency.

Efficacy of Onyx

Technical success was achieved in 9 of 10 patients. In one patient, reflux to the pampiniform plexus persisted after we emptied the maximum amount of 2 vials of Onyx. Then, according to the protocol we completed the embolization with glue. In 6 of the 9 other patients, the occlusion was achieved by one single injection (Fig 1). In the other 3 patients, a second microcatheterization was required. Reflux to the pampiniform plexus persisted through a network of collaterals, which in one case were obscure on the diagnostic venogram (Fig 2). All cases were successfully treated by a second proximal Onyx injection. Therefore complete technical success was achieved in 6 of 10 patients (60%). Mean Onyx injection time was 20 min (range 9-45). The mean amount of Onyx injected was 2.0 cc (range 0.9-3.0). In the group of complete technical success the mean amount of Onyx injected was 1.73 ml during 16.5 min (flow rate 0.11ml/min) versus 2.43 ml during 26.5 min (flow rate 0.11 ml/min).

Five patients found to have a bilateral varicocele were treated at the right side with NBCA-MS.

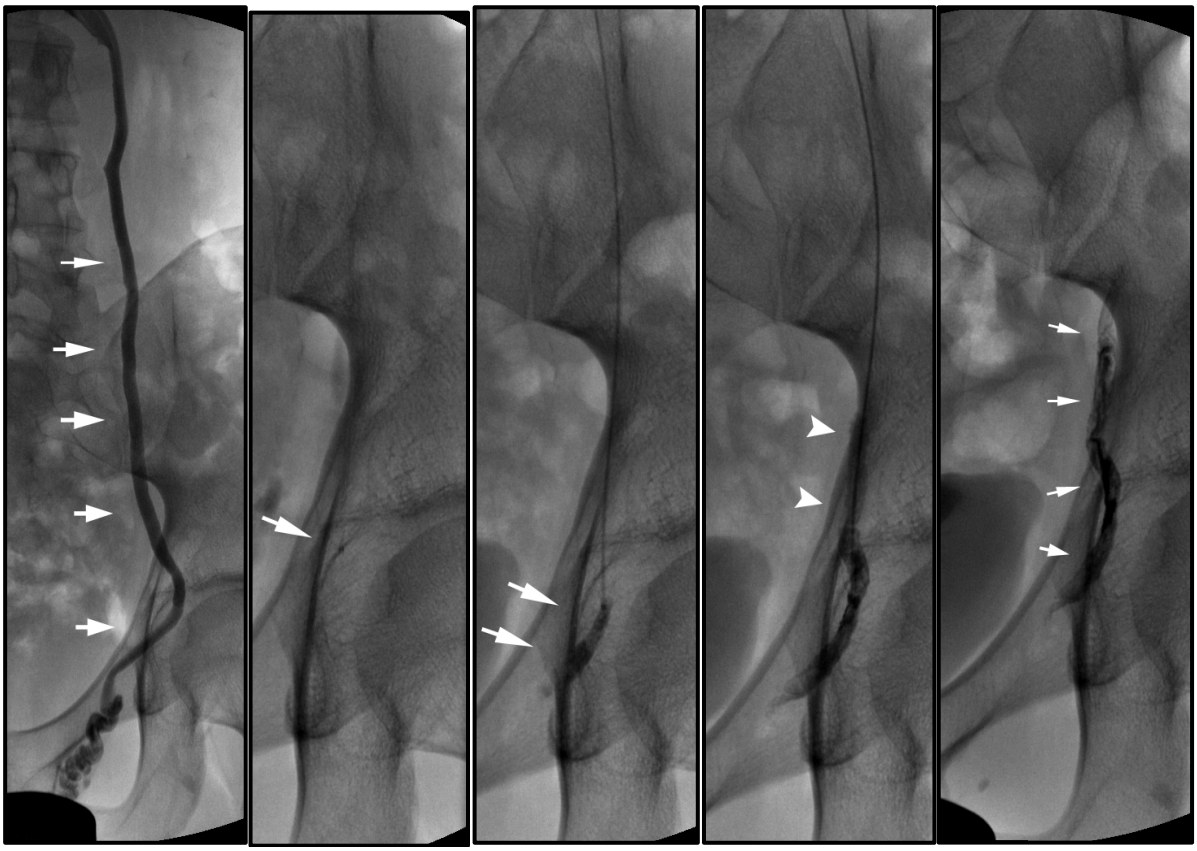
Safety of Onyx

From the moment the Onyx left the microcatheter, distal migration was observed in 2 of the 10 cases. Onyx never entered the pampiniform plexus because we stopped the injection in time or changed the inclination of the Bucky table. Table inclinations therefore varied between 6 and 26°. Ten minutes after completion of the procedure, the Onyx cast remained unchanged. No Onyx migrated in the renal veins or the systemic circulation. Reflux of Onyx around the microcatheter was observed in all patients. Removal of the microcatheter at the end of each injection was easy.

Fig 2 : Case (pt 6) demonstrating incomplete technical success.
Fig 2a : Selective guiding catheter venography in a Bähren type 1 insufficient ISV (arrows).
Fig 2b : Position of the Rebar microcatheter caudal in the ISV (arrow).
Fig 2c : Distal migration of Onyx in the caudal ISV (arrows).
Fig 2d : Reflux of Onyx around the microcatheter (arrowheads)
Fig 2e : Embolic Onyx cast (arrows)
Fig 2f : Selective control venography with persistent opacification of the pampiniform plexus (star), caused by flow through a small paraspermatic branch (curved arrows) that was not visible on the pre-embolization venography. No recanalization of the caudal Onyx cast in the ISV (arrows).

Fig 2g : Second microcatheterization aiming at the small branch, marked by the microguidewire (curved arrows).

Fig 2h : Second embolization with Onyx (arrows) with filling of the collateral network with Onyx.



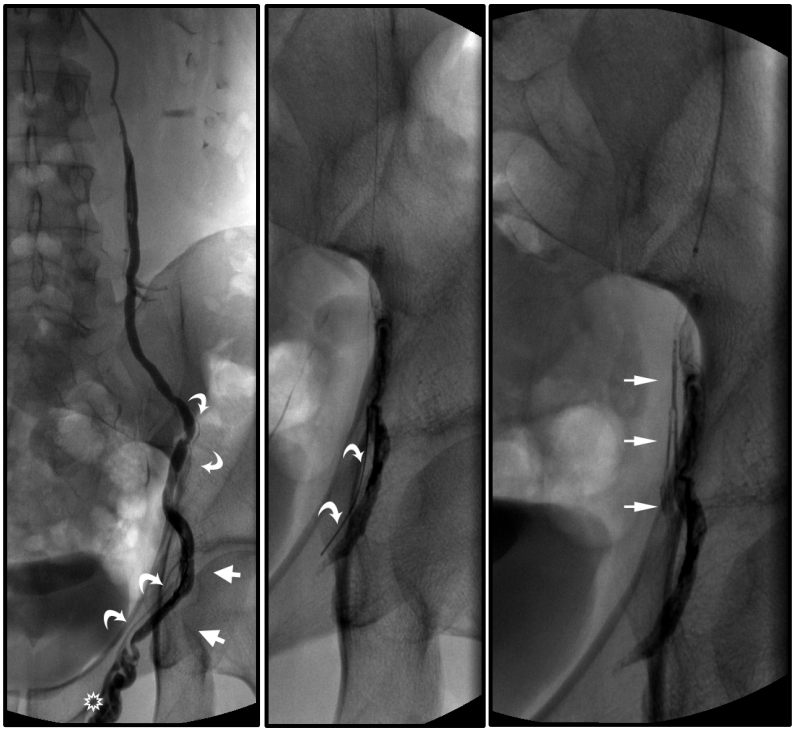


Table 2: Discomfort, amount of Onyx and medication in left spermatic vein embolization with Onyx

patient #	pain*during anesthesia	pain*during embolization	pain*after embolization	pain*1week	embolization medication during embolization	Amount Onyx injected (ml)
1	1	4	1	2	paracetamol	0.87
2	1	2	0	0	None	2.03
3	1	2	1	0	None	1.61
4	1	4	0	0	None	1.63
5	0	4	2	0	paracetamol	1.30
6	1	4	2	1	paracetamol	2.46
7	1	4	0	0	None	1.88
8	1	3	1	0	None	2.96
9	1	1	0	1	None	3.00
10	1	2	0	1	None	2.33

* Pain scale: as in table 1

In 4 patients some Onyx adhered to the microcatheter. In two of them, small Onyx fragments were found in the guiding catheter. There were no blocked guiding catheters after removal of the microcatheter.

A small groin hematoma in one patient and a late allergic reaction to the Iodixanol contrast agent in two patients, were minor clinical complications, unrelated to the use of Onyx. All patient's partners or family members observed a garlic-like smell of breath (caused by the DMSO diffusion) persisting several days after embolization.

The mean fluoroscopy time was 41 min (range 20-65) and the radiation dose 3603.5 cGy.cm2 (range 1270.6-6867.0).

Patient discomfort

During local anesthesia N=9/10 of the patients felt something but had no pain (score 1), one patient had no sensation at all (score 0).

All patients reported discomfort during embolization with Onyx. In four patients the discomfort was overall moderate (score 1-2). The other patients complained of clear to severe pain (score 3-4). Three patients required intravenous analgesics (1 gram Paracetamol, Bristol Myers Squibb, France) (Table 2). Pain started between 10 sec and 6.5 min (mean: 2.7 min) after the appearance of the Onyx in the vein and disappeared after 2-40 min (mean: 25 min).

Analysis of the pain scores revealed that in three patients the pain occurred suddenly, while in the other patients the pain was rather progressive. The pain intensity fluctuated and was associated with the suspension and the restart of the Onyx injection. Only when severe pain was evident, Onyx injection was stopped otherwise it was slowed down. We observed no pain during emptying the DMSO from the “dead space” of the microcatheter. Four patients with a pain score 1 or 2 received a mean of 2.24 ml (1.61-3.00) of Onyx with a mean injection time of 20 min 36 sec, 6 patients with a pain score 3 or 4 a mean of 1.85 ml (0.87-2.96) of Onyx and a mean injection time of 20 min and 11 sec. In other words, mean Onyx injection flow rate was 0.12 ml/min in the first group and 0.10 ml/min in the second group.

Only one of five patients with a right varicocele noticed pain after embolization with glue. This patient complained of a similar pain during Onyx embolization of his left varicocele. After embolization, three patients still noticed some discomfort (score 1), two experienced a bearable pain (score 2) and five were completely well. At discharge from the outpatient clinic, all but one patient (score 1) was symptomless.

Discomfort during one week after embolization

In the week after embolization, 6 patients didn't feel anything abnormal. In three patients some discomfort persisted (score 1). One patient communicated a bearable pain (score 2)(Table 2). Discomfort was located at the inguinal or testicular region, started with a delay of 2 to 3 days and lasted for 1 to 7 days. All 5 patients, who were embolized for a right varicocele with glue, mentioned discomfort (score 1 N=4; score 2 N=1) .

DISCUSSION

This pilot study demonstrated that it is feasible to treat varicoceles with Onyx. However, with the proposed treatment protocol, we encountered technical obstacles and anatomical limitations. First, technical success (embolization with Onyx alone) was achieved in 9 of 10 patients. The technical success rate would have been complete if we had not limited the total amount of Onyx to 3cc. We finished the embolization in this case with glue, but are convinced retrospectively that an additional amount of Onyx would have done the job as well. Secondly, the complete technical success, reflecting best the efficacy of Onyx embolization was less conclusive. In three of our patients, we thought that the Onyx embolus was occlusive and we withdrew the microcatheter. This action proved to be premature, because on the control phlebography reflux was still observed. A second Onyx embolization was required, clearly reducing the efficacy. In all cases we failed to occlude parallel veins and side-branches in one single injection. There are two possible explanations for this failure. First, when the reflux reached the limit of 3 cm, our reflex of gradually withdrawing the microcatheter probably precluded sufficient penetration of Onyx into relevant side-branches. However in 6 of the 10 cases, enough Onyx penetrated into venous connections early before the plug exceeded 3 cm. Secondly, parts of the collateral network were only uncovered after other parts were sealed with Onyx. Opacification of residual bypassing veins by interim contrast injections through the guiding catheter was low, ensuing in these cases a false negative reflux interpretation. After removal of the microcatheter, the flow rate through the guiding catheter even with manual contrast injection was much higher allowing diagnostic venograms. One solution to these technical problems might be the formation of longer reflux plugs in the main vein, which would probably enable a more extensive venous network filling. From this pilot study we know that sticking of the microcatheter in the cast or sticking of Onyx fragment to the microcatheter is not a concern that would hold us back from allowing a longer reflux and injection time.

Because we injected Onyx under local anesthesia we expected a pain reaction, but not as severe and consistent as in this setting of ISV embolization [20]. Nine of 10 patients complained of pain, of whom six showed a severe pain (score 4). In all cases, the Onyx injection was slowed down or even stopped at a certain time. The pursued dynamics of plugging and pushing the Onyx in a continuous column once it appears in side-branches could be lost, and hence, residual venous bypasses might remain patent [27]. In our series the mean amount of Onyx that was injected in patients with severe pain (score 3-4) was clearly lower than in the other patients (1.85 ml versus 2.24 ml). As the mean Onyx flow rate in the painful group was 20% lower than in the other group, pain emanates as an important factor disturbing the embolization dynamics. To what extend pain influenced the final technical result, remains unclear since mean Onyx flow rates between the group with a complete technical success and the other group did not differ (0.11 ml/min). We think that beside pain the aforementioned reasons for incomplete technical results are equivalently important.

DMSO has been nominated as the cause of pain by the distributing company EV3 as well as by several authors [20, 25]. However, pain discomfort started when the Onyx appeared in the vein at the earliest and disappeared slowly after stopping the Onyx injection. There was no pain reaction during emptying the DMSO from the death space of the microcatheter. Every time we restarted the Onyx injection, pain appeared again. In this setting of venous embolization, there is at least some doubt that the pure DMSO provoked the pain. Intravenous anesthesia with Lidocaine particularly if administered in the spermatic vein itself could be a solution for the pain reaction and will be part of a next improved treatment protocol [28]. All 5 bilaterally embolized patients

confirmed the difference in pain sensation between the left-sided (with Onyx) and the right-sided (with Glubran2) embolization. In glue embolization there is no need for intravenous anesthesia because pain, if it occurs at all, rarely intervenes with the embolization act. This observation was again confirmed in our 5 patients treated for a bilateral varicocele, in which the glue embolization at the right side was not disturbed by discomfort.

A favorable behavior of Onyx is that the induced pain was limited to the embolization phase. Afterwards, it was of little clinical concern because 9 of 10 patients reported no pain (Table 2). Again this is in contrast to NBCA-MS, which during the week after treatment was accompanied with a symptomatic inflammatory reaction. An annoying side effect of Onyx is the garlic-like odor, leading to nasty remarks by the family of the patient. Although it's difficult to evoke this smell in advance, patient's partner or family should be informed so that they can eventually prepare for a temporary resettlement.

Radiation burden was higher than in the report by Flacke et al. who embolized the varicocele with coils and sclerosing agents [(29)]. His report counted a mean DAP of 1200 cGy/cm2 with a mean fluoroscopy time of 14 min. In another report by Gazzera et al. the patients were exposed to a much higher mean DAP of 3800 cGy/cm2 for a surprisingly lower mean fluoroscopy time of 5 min [(30)]. Although our fluoroscopy times (mean 41 min) exceeded significantly the above mentioned, the radiation dose was not linearly correlated. We had lower DAP's (3603.5 cGy/cm2) than in Gazzera et al., probably because we only used pulsed fluoroscopy at the lowest frame rate possible. Moreover we had a higher control of the radiation dose by avoiding digital subtraction venography and by taking only single non-subtracted X-ray shots. The longer fluoroscopy times are attributed to the necessity of observing carefully the slow Onyx progression into the vein. Adaptation of the Onyx injection technique by intentionally allowing more reflux and plug formation at the start of the intervention might reduce fluoroscopy time. Moreover, the company might be persuaded to produce Onyx with a higher density, by adding more tantalum, to increase radiopacity.
Until now Onyx is commercial available in vials of 1.5 ml and is, at least in our country expensive and only reimbursed for neuro-interventional indications. For embolization of the spermatic vein, we need at least two vials or 3 ml, which would cost about 2000 Euro, far more than any other embolic agent.

This report is a pilot study limited to 10 patients, conducted to explore the behavior of Onyx in the specific setting of the ISV. No experience with Onyx for venous embolization existed, so we were ignorant how the plug and push technique would work, how pain and discomfort would intervene with it and how high the radiation burden would be. These issues were not completely answered, partly due to the low number of patients included and to the proposed embolization protocol. Although there are alternative and widely accepted agents to occlude the spermatic vein, we think that there is a place for a controllable, well visible, liquid agent to maximize the success of percutaneous treatment of varicoceles. Before we can come to a conclusion about embolization with Onyx in the ISV, further studies will have to solve the issue of discomfort, to find a way to reduce the radiation exposure and to optimize the injection technique.

CONCLUSION

Onyx embolization of varicoceles is technically feasible but remains under investigation because of technical issues and side effects.

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We thank the Ev3 (Covidien) company for the supply of the Onyx vials and the Rebar microcatheters.

‘Conflict of Interest’
The authors declare that the company was neither involved in the study protocol, the analysis of the results, nor in the writing of the manuscript.

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Preface to part 1.4

Percutaneous glue embolization has the advantage of being an outpatient procedure with a faster return to normal activities and a considerable lower cost and lower recurrence rates than surgery [1-3].

However, catheterization and embolization during the procedure need the use of X-rays. Therefore, the radiation exposure must be kept as low as reasonably achievable (ALARA principle) [4]. Because almost all percutaneous varicocele embolizations are performed in adolescents and young healthy men with normal life expectancy (range 12-30 years), special attention should be paid to radiation dose optimization. In fact, the latter patient group is more vulnerable to radiation-induced malignancies in comparison with the average population[4].

Literature data on the radiation exposure during varicocele embolization is rather scarce. In most of these studies a risk estimation of cancer induction and hereditary effects is performed. In general, radiation doses and associated radiation risks were found to be within the range of other diagnostic procedures, such as computed tomography and nuclear medicine procedures [5-7]. However, these results were based on effective dose calculations in standard-sized mathematical models of the patient's anatomy. The latter models do not necessary represent the size of the treated patients. Moreover, the effective dose is not appropriate as quantity to assess radiation risks of individual patients [4]. In particular, the effective dose for an individual male patient does not exist, as a gender averaging procedure is to be carried out for the calculation of this quantity!

In a prospective study, exposure parameters (such as DAP, kVp, beam filtration) used during endovascular treatment of varicoceles were registered. In addition, skin and testis doses were measured in-vivo by means of thermoluminescent dosemeters. To obtain accurate organ dose estimates, a patient-specific Monte-Carlo simulation was set up using mathematical phantoms scaled according to the size of the actual patient. As a result a detailed overview of the radiation exposure during endovascular varicocele embolization procedures was obtained (aim 1&6). Afterwards, organ doses were converted into a cancer risk by means of the age, gender and organ specific cancer risk models of the National Academy of Sciences Advisory Committee on the Biological Effects of Ionizing Radiation [8]. The latter risk estimates are important to assess whether fluoroscopy-guided embolization of varicoceles is safe.

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4. 1.4 Radiation exposure related to the fluoroscopy guided embolization of varicocele

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ABSTRACT

PURPOSE: To assess the radiation dose and associated risks after fluoroscopy guided embolization of varicocele.
MATERIALS AND METHODS: The study population consisted of 20 male patients, who underwent an embolization procedure for treatment of varicocele (median age of 19.5 years). Peak skin doses and gonadal doses were measured in-vivo using LiF thermoluminescent dosemeters. Patient-specific organ doses were calculated by means of a Monte Carlo simulation. Risks for x-ray induced malignancies in the patient population under study were estimated by means of the age, gender and organ specific cancer risk models of the National Academy of Sciences Advisory Committee on the Biological Effects of Ionizing Radiation.
RESULTS: Peak skin doses after the embolization procedure were low (median value: 98 mGy) and far below the threshold for deterministic skin effects. A significant correlation between peak skin dose and DAP was found. A median testes dose of 0,34 mGy was found, corresponding to a median risk for hereditary effects of about 2 per million. The applied gonadal shield reduced the testes dose with about 40%. The median risk for cancer mortality was quantified to be 0.05%.
CONCLUSION: When using the appropriate radiation protection and optimization measures, such as the use of pulsed fluoroscopy, accurate beam collimation and gonadal shielding, x-ray doses and associated risks were assessed to be very low for the embolization procedure of varicocele.

KEYWORDS: Varicocele / Embolization / Radiation dose/ Radiation risks

INTRODUCTION

Varicoceles consist of abnormally dilated veins in the pampiniform plexus of the scrotum, caused by reflux of blood in the internal spermatic vein[1]. Varicoceles are detected in approximately 15% of the adolescent male population, in up to 45% of men with primary infertility and in up to 80% of men with secondary infertility[2-4].The abnormality is extremely rare in boys before the age of 10 years.

Although etiology and pathophysiology is probably multifactorial, anatomical variations of the internal spermatic vein, internal spermatic reflux secondary to congenital and/or acquired valve dysfunction and left renal venous obstruction by the "nutcracker effect" are among the most accepted[5,6].

Treatment is indicated because of local discomfort or male infertility and reduced sperm quality[7-9] Treatment of varicoceles for infertility or to prevent infertility remains controversial, because the majority of men with varicoceles are still fertile. American and European urological and reproductive societies recommend varicocele treatment only for patients with clinical varicoceles and abnormal semen analysis or for adolescents with testicle hypotrophy.

Treatment consists of interruption of reflux through the internal spermatic vein and its branches superior to the pampiniform plexus. This can be achieved either by surgical as by percutaneous endovascular techniques. Percutaneous embolization has the advantage of being an outpatient procedure with a faster return to normal activities and a considerable lower cost and lower recurrence rates than surgery[10-12].

However, percutaneous embolization needs X-rays to perform the selective venography and to deliver the embolic material. Several papers deal with patient x-ray doses of embolization procedures for treating varicocele[13-20]. Most of them present measured testes doses and effective dose calculations in standard-sized mathematical models of the patients anatomy, using the calculation methodology of the by now outdated ICRP 60 publication[21]. The latter models do, however, not necessary represent the size of the treated patients. Moreover, the effective dose is considered as not appropriate as quantity to assess radiation risks of individual patients[22].

To this end a patient-specific Monte Carlo simulation of the complete procedure for each patient was performed. Risks for x-ray induced malignancies in the patient population under study were estimated by means of the age, gender and organ specific cancer risk models of the National Academy of Sciences Advisory Committee on the Biological Effects of Ionizing Radiation[23]. In addition, the radiation reducing effect of a 1 mm lead shield protection around the scrotum was investigated.

MATERIALS AND METHODS

Patients

The study population consisted of 20 male patients, who underwent an embolization procedure for treatment of varicocele (Table 1). The median age was 19.5 years (range: 12.0 – 44.0 years). Age of half of the patients was younger than 20 years. These patients were adolescents presenting with varicocele without pain or discomfort. Most of the remaining patients (8 of 20) were treated for a varicocele because of infertility. Two remaining patients were treated for other reasons, of which one patient complained about pain and discomfort. Five patients had clinically bilateral varicocele.

X-ray embolization procedure

All procedures were performed with an Axiom Iconos R200 x-ray system (Siemens, Erlangen, Germany). Tube settings such as peak voltage and anode current are controlled by the automatic brightness control. Right transfemoral catheterizations were performed using semi-automatic pulsed fluoroscopy (3pulses/second) to keep radiation as low as possible. Before embolization, selective venographies of the renal veins, and at the proximal and distal segments of the insufficient internal spermatic vein were done. During glue embolization, pulsed fluoroscopy was increased (15pulses/second) to improve visualization. After embolization the glue embolus was documented and a control venography of the renal and spermatic vein was performed. All radiographies during the procedure were documented that x-ray exposure was limited to the hypochondrium and the groin. All patients received a 1 mm lead shield protection around the scrotum (Testes capsule TK, Dr. Goos-Suprema)[24].

Acquisition of exposure parameters

The dose-area product (DAP) was measured with transmission ionization chambers (PTW, Germany) attached to the x-ray tube and connected to a Diamentor M4 readout unit (PTW, Germany). The DAP meter was calibrated on site using a large-area reference DAP meter (patient dose calibrator, PDC, Radcal). The energy response of this instrument is markedly lower than that found with conventional DAP meters, thereby reducing the uncertainty in DAP calibration to less than 5% [25].

For each image acquisition series used in the procedure, position of the x-ray tube, source-to-image-intensifier distance, field size, tube potential and fluoroscopy time were recorded for all patients. DAP data for each fluoroscopy run and spot image were gathered by connecting the Diamentor M4 readout unit to a laptop and using software written in-house as described earlier[26]. In Table 1 the exposure parameters of the treated patients are summarized.

Measurement of peak skin dose and testes dose

To measure the peak entrance skin dose from the x-ray exposures, an array of 9 LiF TLD-100 (Harshaw, Bicron) was attached to the skin of the patient on the radiated part of the abdomen, which extends from the kidneys to the pelvis. Two LiF TLD-100H (Harshaw, Bicron) were placed

at each of the testis, underneath the lead protection, to directly assess the gonad dose. The latter TLDs have a higher sensitivity, compared to TLD-100 as the doses were expected to be very low. To assess the influence of the lead shield, 4 TLD-100H detectors were attached on the lead shielding as well.

All TLDs were analyzed by a Harshaw 3500 reader (Harshaw, Bicron). All TLDs were calibrated at the same beam quality that was used in situ. The SD within the set of TLDs was minimized to 2%. The gonad dose was calculated as the mean dose reading of the four TLDs. To assess the testes dose without shielding, the mean TLD doses on top of the shielding were corrected for the difference in backscatter between lead and tissue. The measured testes doses also served as a verification of the results of the Monte Carlo simulation.

Monte-Carlo simulation model

A patient-specific Monte Carlo dose simulation was set up to analyze the radiation dose received by the corresponding patient. First, a mathematic male anthropomorphic phantom was generated based on the body length and weight of the individual patient, using an in-house developed software tool as described in a previous study [26]. The phantom calculation was based on the interpolation between the revised ORNL phantoms [27]. Subsequently, the recorded irradiation geometry of the x-ray tube together with the field size and the x-ray spectral distribution used for a particular projection in a patient was implemented within the computed phantom. The x-ray spectra were calculated with an analytical program [28]. The final computer model was used as input for the MCNP-X 2.5.0 Monte Carlo simulation code.

Calculation of organ doses and 'pseudo effective dose'

For every x-ray exposure within the embolization procedure, equivalent organ and tissue doses per unit of DAP were simulated with the Monte Carlo code. By multiplying these values by the corresponding recorded DAP, the total equivalent organ and tissue doses of a complete procedure were obtained.

As the effective dose is a protection quantity for assessing the radiation burden of a gender averaged reference person, calculation of the latter quantity for our male population is in principle impossible[22]. Moreover, the effective dose should not be used for individual radiation risk assessments[22]. Nevertheless, for comparison purposes only, a 'pseudo effective dose' was calculated as a weighted summation of the obtained male equivalent organ doses with the corresponding tissue weighting factors of the ICRP 103 publication[22].

Risk estimation

Lifetime attributable risks (LAR) of cancer mortality associated with the embolization procedure of every individual patient were calculated according to the BEIR VII risk models for different cancer types, taking into account age-dependent incidence and mortality rates within the Euro-American population [23]. Inputs for these risk assessments were the simulated organ doses and the age of the individual patients. The LAR data from BEIR VII were adapted for a dose and dose-rate effectiveness factor of 2 as proposed by the ICRP [22].

For the estimation of hereditary effects, the measured testes doses were multiplied with a risk factor of 0.54%/Gy, as advised in the latest recommendations of the ICRP[22].

RESULTS

Demographic patient data and exposure parameters used during the embolization procedures are summarized in Table 1.

Measured peak skin doses after the embolization procedure were generally low (median value: 98 mGy). Even for a very complex procedure with a prolonged fluoroscopy time of 52.7 min, the measured peak skin dose (911 mGy) was still far below the threshold for deterministic skin effects.

A median measured testes dose of 0.34 mGy was found, corresponding to a median risk for hereditary effects of 1.8 per million (range 0.2 – 21.1 per million). Taking into account the dose readings of the TLDs positioned on top of the lead shield, and correcting them for the difference in backscatter, a shielding dose reduction factor of 40% was found.

Both measured peak skin dose and testes dose correlated significantly with DAP ($p<0.01$). This correlation was found to better for the peak skin dose (Figure 1A) than for the testes dose (Figure 1B). The latter can be explained by the fact that TLDs for assessing the peak skin dose were directly in the x-ray beam, whereas the testes TLDs mainly measured scattered irradiation.

By means of a patient-specific Monte Carlo simulation, equivalent organ doses for all patients were calculated. Comparison of the measured and simulated testes doses showed an excellent agreement (Figure 2) between the latter values, indicating a correct simulation set-up of the procedures.

As most published studies rely on the calculation of the effective dose, for comparison reasons, a 'pseudo effective dose' was calculated for our patient population. A median value of 1.3 mSv (range 0.3 – 4.6 mSv) was found.

Based on the Monte Carlo calculated organ doses, individual LAR values for cancer mortality according to the BEIR VII risk models were calculated for every patient. The BEIR VII report provides a method to estimate LAR of cancer mortality based on the organ doses associated with the radiation exposure and a patient's age at the time of exposure. The median risk for cancer mortality was quantified to be 0.05% (range 0.02 – 0.17%). The correlation between LAR and the pseudo effective dose is presented in Figure 3. An overall mortality risk factor of 4.1%/Sv was found for radiation-induced malignancies in our patient cohort.

DISCUSSION

Because almost all percutaneous varicocele embolizations are performed in adolescents and young healthy men with normal life expectancy, special attention should be paid to the justification and radiation dose optimization of these procedures. In fact, the latter patient group is more vulnerable to radiation-induced malignancies in comparison with the average population[22,23,29]. Therefore an accurate estimate of patient radiation doses and associated risks is important.

Published exposure and dosimetry data of varicocele embolization procedures are summarized in Table 2. The value of fluoroscopy time obtained in our study (median value of 19.5 min) correspond with the previously published mean and median values, ranging from 6.1 to 30.4 minutes[13-20]. When dividing the total DAP with the corresponding fluoroscopy time, however, we observe a remarkably lower value in current study as compared to others. The latter is probably due to the systematic use of pulsed fluoroscopy (down to 3 pulses/second) and the careful collimation of the x-ray beam to minimize the irradiated surface of the patient.

The risk for a skin injury is related to the peak skin dose value[30]. The maximum skin dose measured in this study (911 mGy) was far below the 2-Gy threshold level for transient erythema. The latter value corresponded with an extremely large fluoroscopy time in a complex procedure. The median peak skin dose of 98 mGy in our study may be compared with previous (mean) values of 73 mGy[17] , 131 mGy[18] , 148[20] and 210[16] mGy. Because of the moderate values of skin doses, radiation-induced skin injuries are unlikely for embolization procedures of varicocele. On the other hand, skin dose has to be monitored so that the interventional radiologist knows the maximum skin dose delivered during the procedure. Because the DAP correlates very well with peak skin dose (Figure 1A), DAP measurement is suitable for online skin dose estimation.

Published testes dose vary considerably, with mean values ranging from 0.01 mGy[13] up to 14.8 mGy[14]. In our study a median value of 0.34 mGy was found. Measurement of testes dose is rather difficult as the latter dose is mainly due to scattered irradiation and therefore results in very low dose values. Appropriate high-sensitivity dosimeters should be used to tackle this problem. In addition, a slight variation in dosimeter positioning, might change the measured value low dose considerably. In our study, the quality of the measurement was guaranteed due to a good agreement between the measured testes doses with those obtained by means of Monte Carlo simulations (Figure 2). Even though the testes doses are very low, the application of a lead scrotum shield is useful. Our data suggest that a 40% dose reduction is obtained due to the latter shielding. In other studies it is mostly unclear whether shielding was used or not.

In publication 103, ICRP is giving a risk coefficient of 0.54%/Gy for the reproductive population. The latter factor includes hereditary effects such as Mendelian diseases, chronic diseases and congenital abnormalities, expressed over two generations[22]. The application of the latter risk factor resulted in our study population into a very low risk for hereditary effects of 1.8 per million. This value is comparable with the median risk values of 1.08 and 2.4 per million found by Chalmers et al [15] and Calama et al [19] respectively.

Most authors also present an estimate for the quantity effective dose. However, the latter quantity is not appropriate for individual patient dose assessment as, in principle, effective dose represents a gender-averaged dose value[22]. For comparison purposes only, we calculated a ‘pseudo effective dose’ as a weighted summation of the individual Monte Carlo simulated male equivalent organ doses with the corresponding tissue weighting factors of the ICRP 103 publication[22]. Our calculations resulted in a median value of 1.3 mSv, which is low in comparison with other interventional X-ray procedures[31]. Previously published effective dose values vary from 0.7 to 34.5 mSv[13-20]. It should be noted that all of these values are based on the outdated tissue weighting factors of ICRP publication 60[21].

For all patients a patient-specific risk estimate for radiation-induced cancer mortality was calculated based on the simulated equivalent organ doses of the individual patients and the BEIR VII risk models. The latter model provides cancer mortality risks for different organ sites for a male and female population separately and take the age at exposure into account[23].

In present study, a median value of 0.05% was found for radiation-induced cancer mortality risk, which corresponds to an overall risk factor of 4.1%/Sv. Chalmers et al. found a median cancer risk of 0.013%[15], whereas Calama presented a median value of 0.04%[19].

In conclusion, when using the appropriate radiation protection and optimization measures, such as the use of pulsed fluoroscopy, accurate beam collimation and gonadal shielding, x-ray doses and associated risks were assessed to be very low for the embolization procedure of varicocele. According to the NCRP publication 168, the obtained risks in our study population are requiring a "minor to moderate benefit for the patient" to justify the varicocele embolization procedure [32].

Table 1: Demographic patient data and exposure parameters of patient group (n=20)

Demographic patient data	
Age, y	19.5 (12.0 – 44.0)
Weight, kg	62.5 (40.0 – 88.0)
BMI, kg/m²	21.2 (16.0 – 28.4)
Exposure parameters	
Fluoroscopy time, min	19.5 (10.6 – 52.7)
Total DAP, cGycm²	491.5 (123.5 – 2988.1)
Peak voltage of acquisitions, kVp	78.0 (70.0 – 85.0)
Used copper filtration, mm Cu	0.1 (0.0 – 0.2)
Number of spot acquisitions, n	13 (9 – 32)

BMI=body mass index; DAP=dose area product. Values represent the median (range).

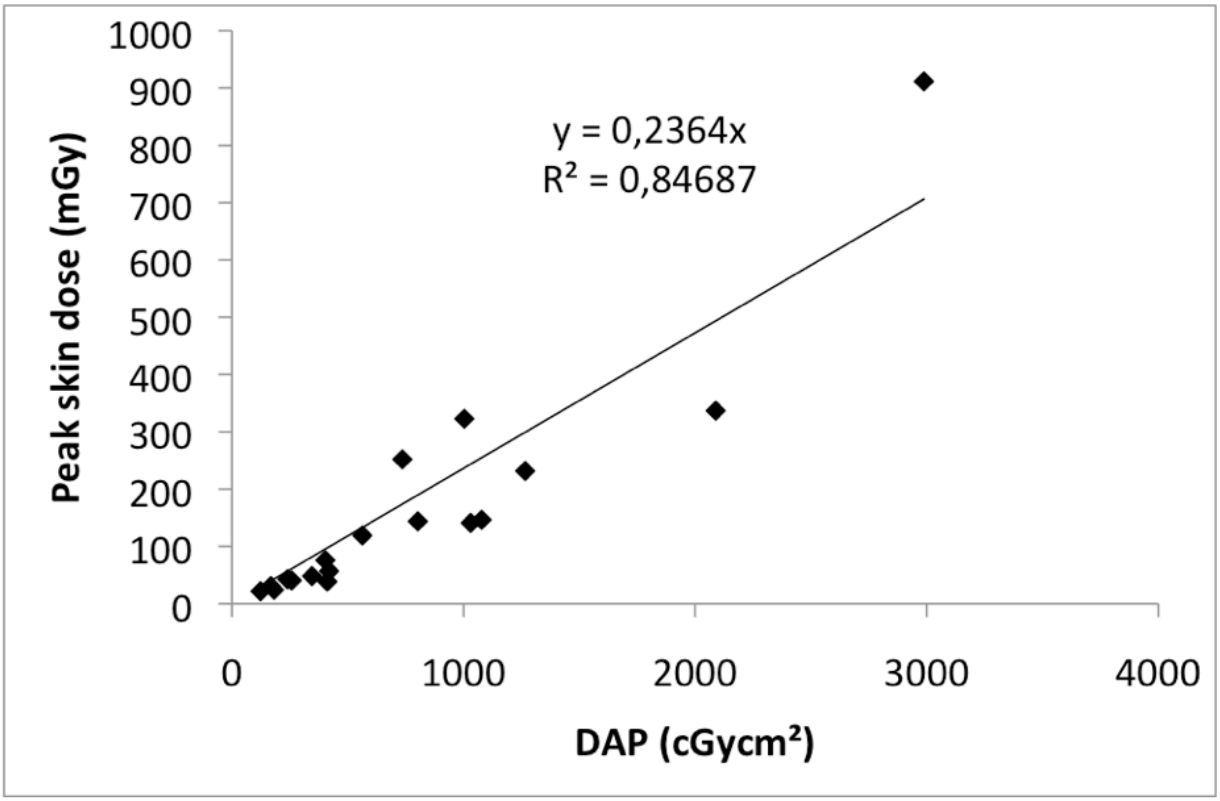
Table 2. Dosimetry results related to fluoroscopy guided embolization of varicocele. Comparison of published data with results obtained in current study.

Reference	Fluoroscopy time (min)	DAP (Gycm²)	Peak skin dose (mGy)	Testes dose (mGy)	Effective dose (#) (mSv)
Rieger J et al. (1996) [13](*)	6.1	4.1		0.01	
Ruiz-Cruces R et al. (1997) [14](*)	30.4	106.3		14.8	34.5
Chalmers N et al. (2000) [15]($)(£)	5.2	5.7		0.05	0.7
Pieri S et al. (2003) [16](*)	8.7		210	6.7	21.6
Miller et al. (2003) [17](*)	10.3	12.9	73		
Gazzera C at al. (2006) [18](*)	6.3	38.4	131	0.49	5.2
Calama Stantiago JA et al. (2006) [19]($)(£)	15.7	13.1		0.1	1.9
Jensen K et al. (2011) [20](*)(%)	11	11	148		
Current study					
Median	19.5	4.9	98	0.34	1.3
Mean	24.2	7.7	166	0.64	1.5
Min	10.6	1.2	4	0.04	0.3
Max	52.7	29.9	911	3.90	4.6

(*) Values represent the mean.
($) Values represent the median.
(£) Data taken from the prospective study of the author.
(%) Data taken from the flat-panel system.
(#) Effective dose values from current study represent a 'pseudo-effective' dose, for comparison purposes only.

Fig 1: Correlation between DAP and peak skin dose (A) and measured testes dose (B)

A



B

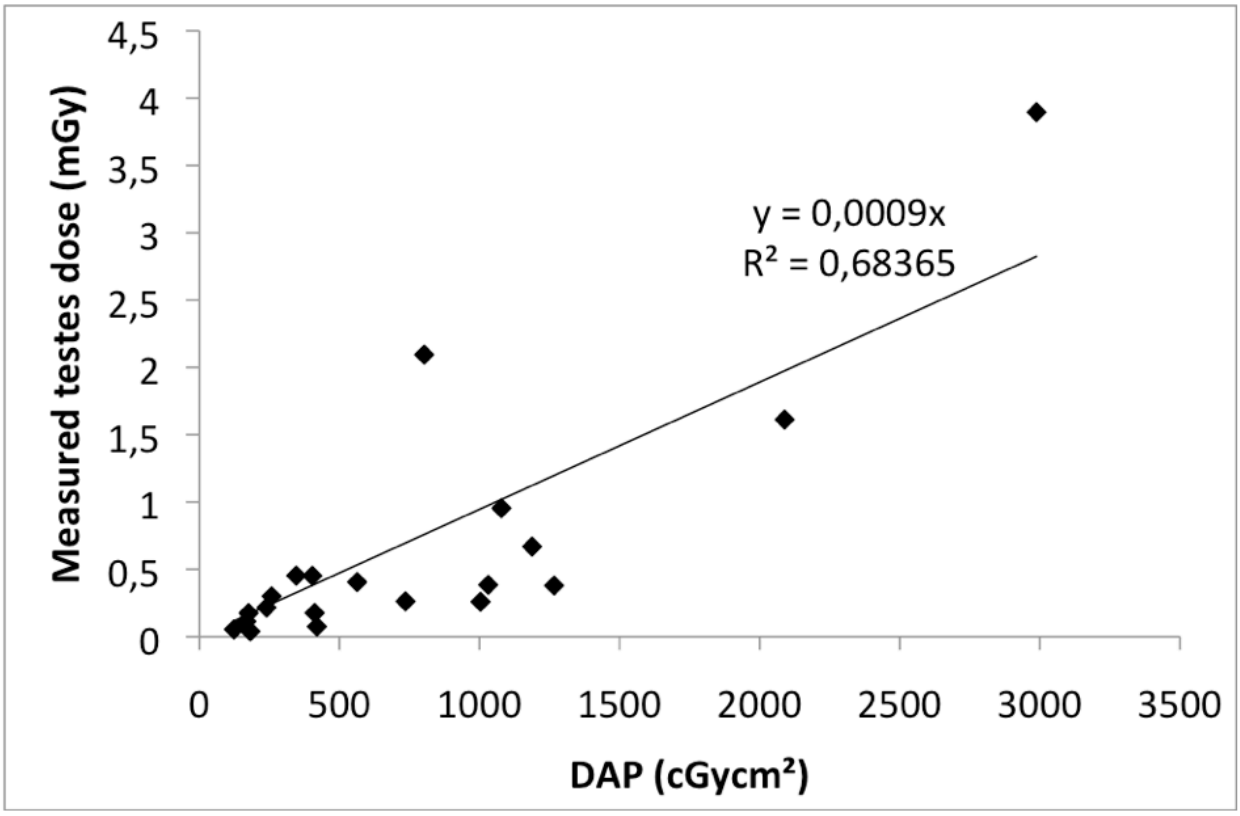


Fig 2: Correlation between Monte Carlo simulated and measured testes dose.

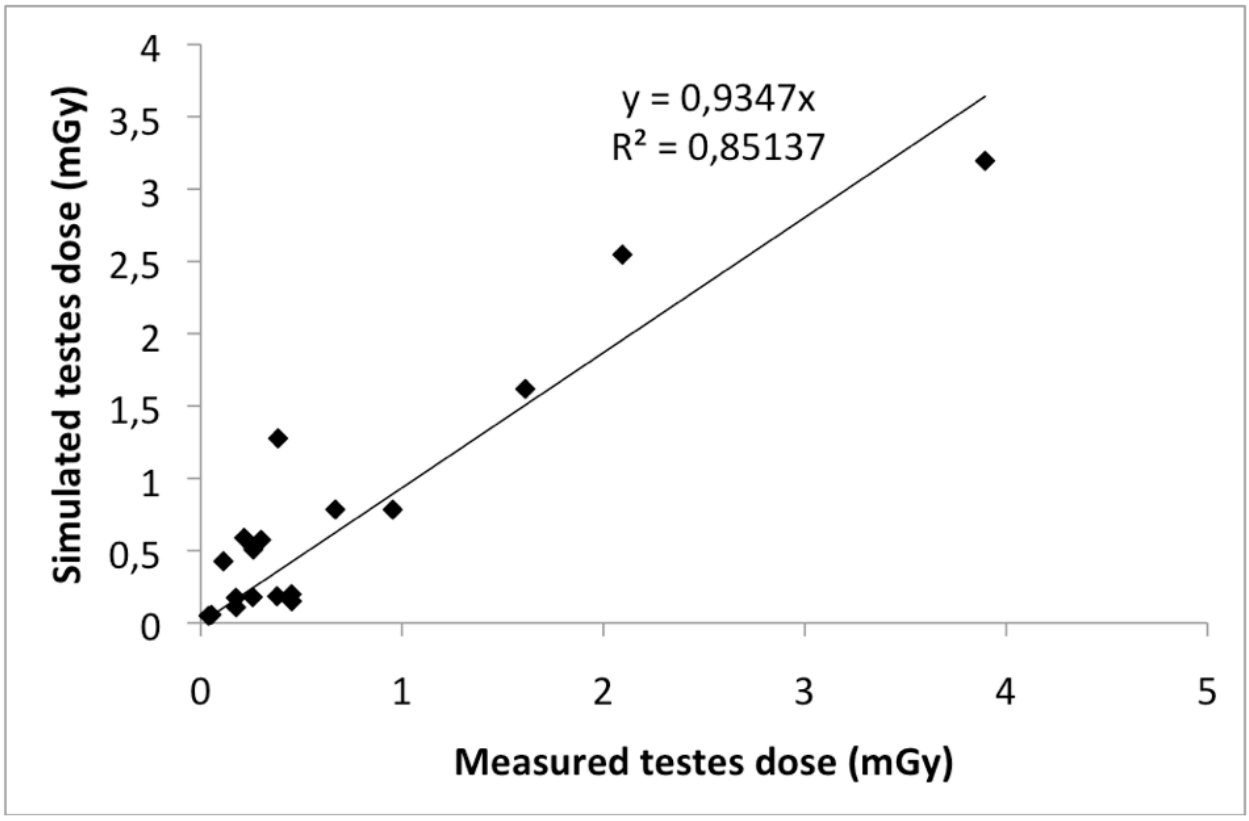
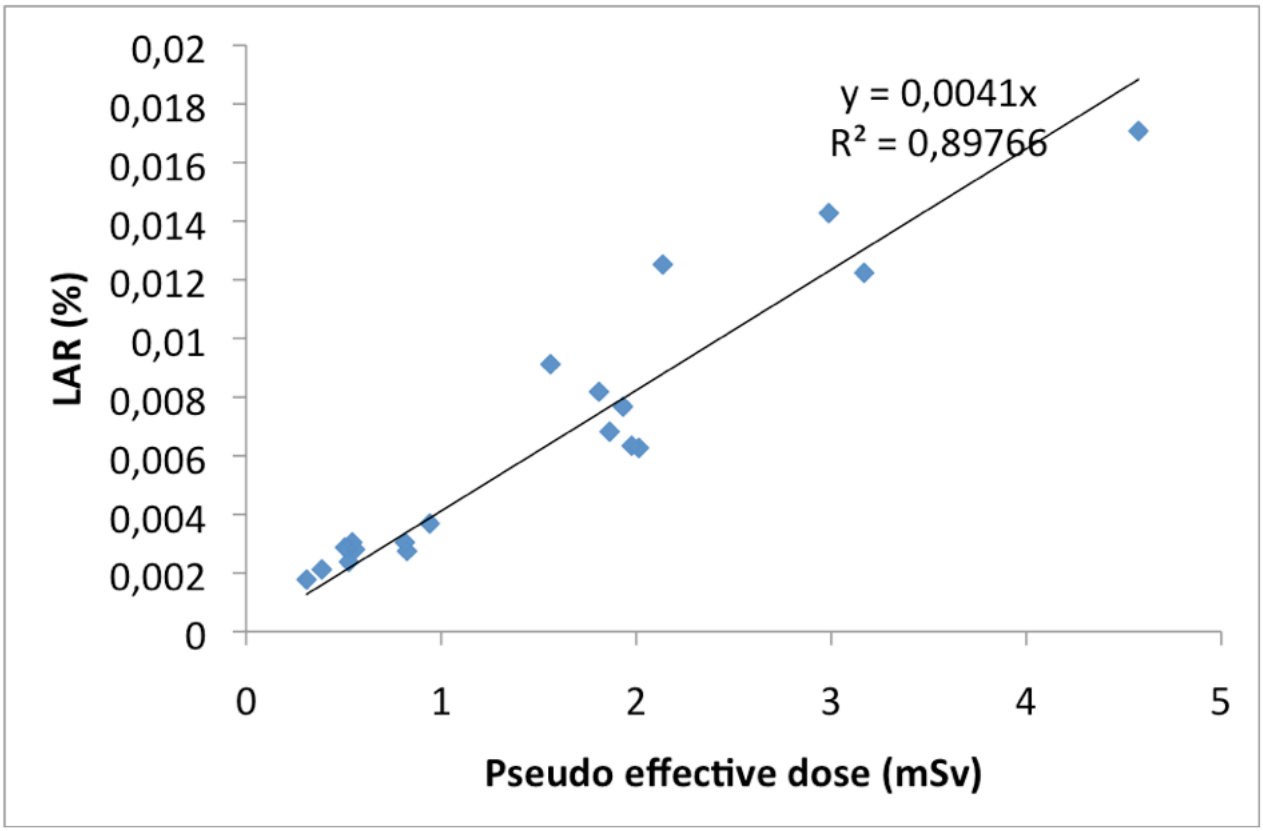


Fig 3: Correlation between life-time attributible risk (LAR) and ‘pseudo effective dose.



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4.Part 2 Anatomical phlebographic aspects and fluid behavior in varicoceles

Preface to part 2.1

At a certain moment in my practice, I had the impression that varicocele embolizations in adolescents seemed a technically more straightforward procedure than in adults and that the procedure in adolescents lasted less long. In my opinion, the reason for this was the presence of more competent outflow valves and a more complex anatomy of the ISV in adult patients. These observations might correspond with a different phlebographic anatomy of the ISV between adolescents and adults, and could discover a different pathophysiology of varicoceles.

To investigate these observations and to discover a possible difference in pathophysiology between adolescents and adults, we set up a blind retrospective study in which we compared all major phlebographic radio- anatomical landmarks between both groups (aim 2&7/8). Phlebographies of consecutive varicocele embolizations were anonymized and those of patients from 17 to 24 years old were excluded to ensure two populations that are distinctly adolescent or distinctly adult.
The radio-anatomical landmarks were based on all possible differences we ever observed on phlebographies of the right and left ISV. We included also the most appropriate phlebographic classifications for the left (Bähren) and right (Siegel) varicocele.

4. 2.1 Internal spermatic vein insufficiency in varicoceles: a different entity in adults and adolescents?

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ABSTRACT

PURPOSE:

To find out whether phlebographic landmarks could discriminate adult from adolescent varicocele.

METHODS AND MATERIALS:

Left and right internal spermatic venograms of 191 adolescents (< 17 y) and 224 adults (≥ 25 y) were anonymized and evaluated. Phlebographic radio-anatomic landmarks (valves, duplications, collaterals and classifications) were compared and analyzed with univariate tests.

RESULTS:

Insufficiency of the left internal spermatic vein (ISV) was confirmed in all patients, except in 6 adults. Adults had 2 times more frequently no spontaneous opacification of the ISV during venography (P=0.001), 2.2 times more often a complex outflow into the renal vein (P=0.021) and significantly more collaterals (P=0.030). Adolescents had a significantly lower number of competent valves and significantly more often a nutcracker phenomenon (P=0.001). Applying the Bähren classification, the distribution of the types of ISV's was significantly different between adults and adolescents (P=0.009).

Insufficiency of the right ISV was encountered 2.5 times more frequently in adults (P< 0.001), in whom the maximum diameter of the ISV was significantly larger (P=0.023). Bilateral ISV insufficiency was 2.3 times more often encountered in adults (P<0.001).

CONCLUSION:

No clear-cut veno-anatomical base was found to distinct adult from adolescent varicoceles. Some characteristics point at congenital forms of left varicoceles in adolescents. In adults, reflux is likely to be induced via collateral pathways. For right ISV insufficiency, we found arguments that the adult varicocele might be a late stage form of the adolescent varicocele.

KEYWORDS: varicocele-adolescents-adults-phlebography-pathophysiology

INTRODUCITION:

Varicoceles are abnormally dilated veins in the pampiniform plexus (PP), caused by reflux of blood in the internal spermatic vein (ISV)[1]. Anatomical variations in the drainage of the ISV, congenital or acquired valve dysfunction and left renal venous obstruction by the "nutcracker effect" are among the most accepted etiologies [2,3].

Varicoceles are first diagnosed in puberty with an incidence of about 15%. The incidence increases up to 45% and 80% in males consulting for primary and secondary infertility respectively [4-6] The association of varicoceles and testicular hypotrophy or growth arrest varies widely from 10 to 70% in adolescents and is found in 30% of adults [7-9]. It's not clear whether the testicular hypotrophy in adults is an evolutive variant of the hypotrophy encountered in adolescents and whether the varicocele in those adults existed since childhood or developed later on as a distinct identity. Although varicocele treatment results in testicular "catch up growth" and in improvement of the sperm, varicoceles and infertility remain a subject of controversy [10-13].

Another difference is that children are mostly referred for an asymptomatic varicocele and adults present with either infertility or local discomfort.

Adult varicocele could be the final stage of a progressive disease that starts in adolescence. Then phlebographic abnormalities in adolescents and adults would be similar, albeit with more pronounced venous dilatation or with a higher number of insufficient valves at a later stage.

At one point in our practice of endovascular treatment we suspected differences in the anatomy of the ISV between adolescents and adults. Competent valves and side channels seemed to interfere with the technical approach more often in adults than in adolescents. ISV embolization in adolescents seemed more often a straightforward procedure, accomplished in less time than in adults. These uncontrolled observations would be indicative for a difference in the phlebographic anatomy, and particularly against a progressive disease.

To substantiate a putative difference in pathophysiology, we retrospectively compared radio-anatomical characteristics of the ISV in adolescents and adults referred for varicocele embolization.

Fig 1: Type 1 insufficient ISV according Bähren (age: 16 years, with a left overt varicocele).
Fig 1a: Left RV phlebography demonstrates a single insufficient outflow valve (arrowhead) and spontaneous visualization of a solitary (arrow) insufficient ISV (arrows). Nutcracker phenomenon is absent (curved arrow). Outflow angle is 75°, largest diameter is 3.7 mm.
Fig 1b: Selective ISV phlebography shows medial collaterals (curved arrows) and paraspermatic veins (arrowheads).

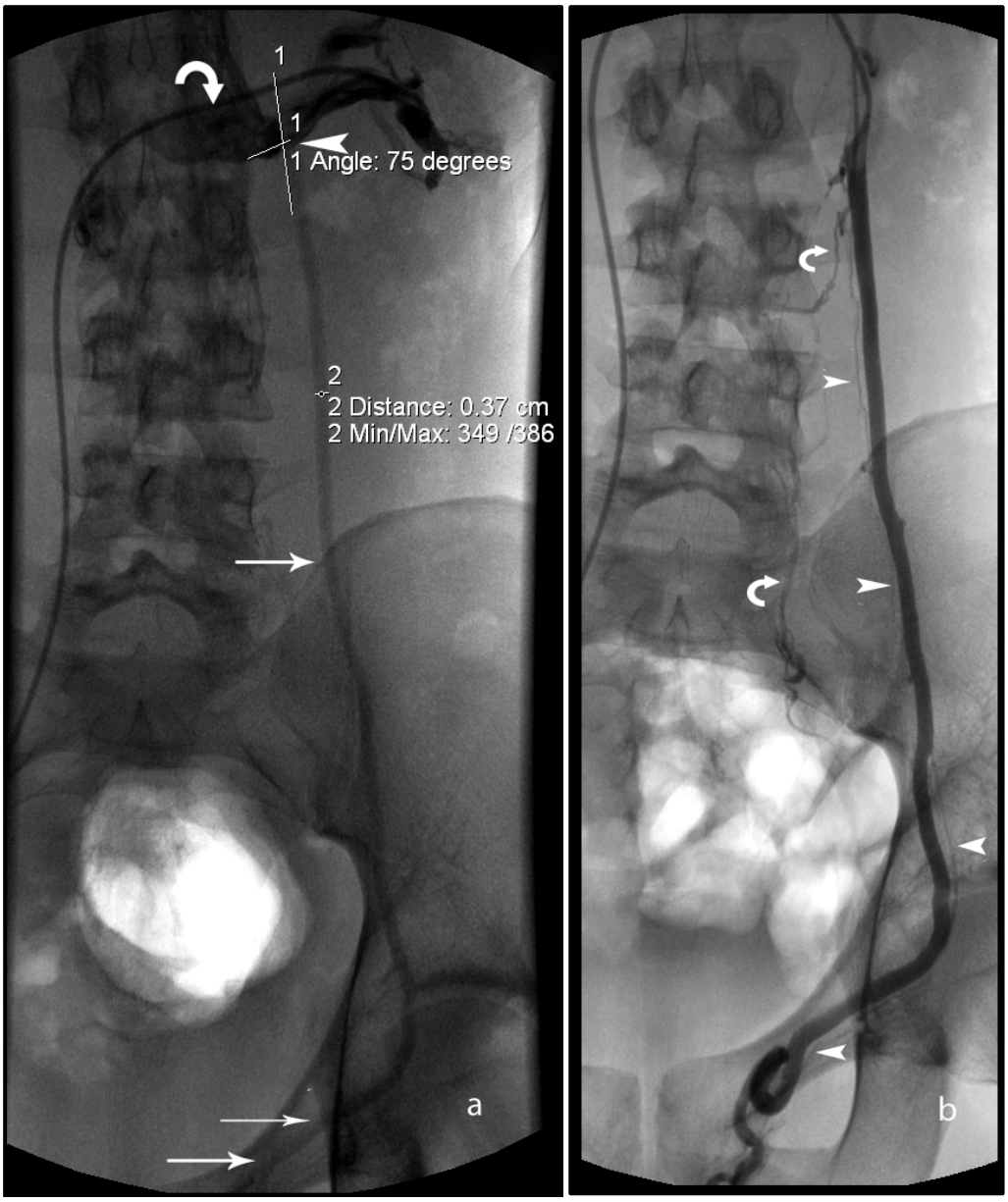


Fig 2:Insufficient left ISV type 5 according Bähren and right ISV type 4a according Siegel (age: 12 years, bilateral overt varicocele).
Fig 2a: Left RV phlebography with a double RV (arrowheads) and a spontaneous visualization of a solitary ISV (arrow). Compression by an anterior and posterior (mixed) nutcracker phenomenon (curved arrows) was observed.
Fig 2b: Left RV phlebography with a single competent outflow valve (arrow) and spontaneous ISV visualization (arrowhead) through a reno-spermatic bypass (double arrows). Small lateral collaterals (curved arrow) are visible.
Fig 2c: Right RV phlebography with an insufficient single outflow valve from the RV (arrowhead) and spontaneous visualization of the ISV (arrow).
Fig 2d: Selective ISV phlebography revealed an ISV insufficiency (arrow) with lateral collaterals (curved arrow) and multiple duplications of the ISV (arrowheads).

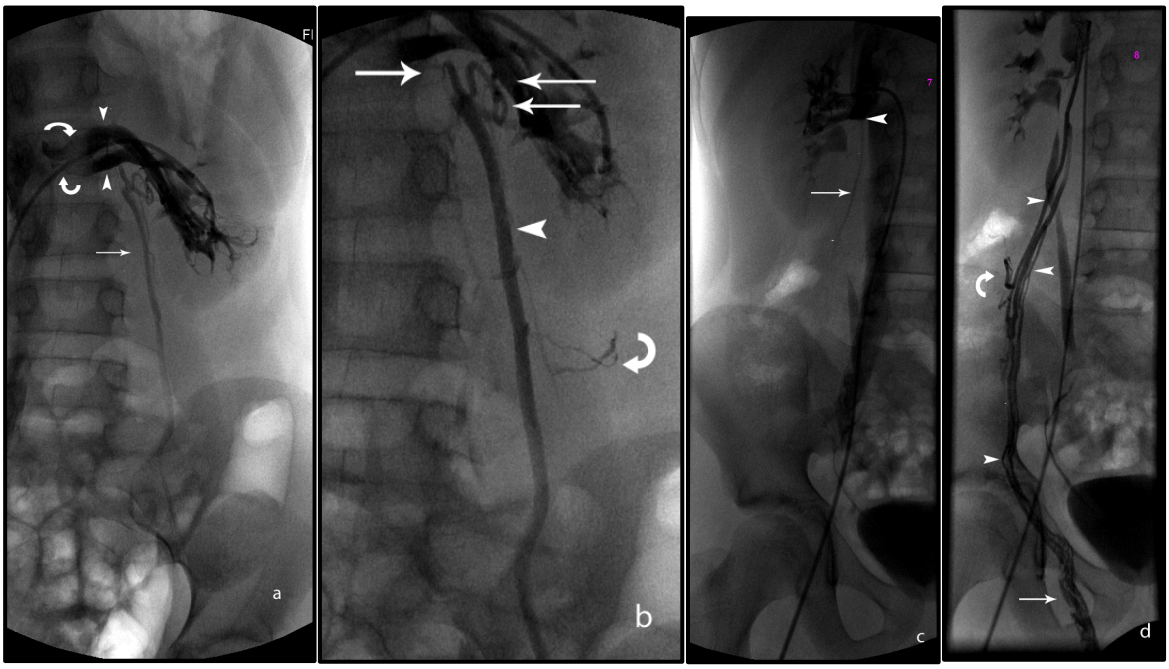


Fig 3: Insufficient right ISV type 4 Siegel (age: 16 years, bilateral overt varicocele).
Fig 3a: Right RV phlebography with competent outflow valves from the RV (arrow) and the caval vein (arrowhead).
Fig 3b: Selective ISV phlebography revealed an ISV insufficiency (arrow) with a broad medial collateral (curved arrow) and a solitary ISV (arrowhead) with an outflow in the RV and in the caval vein according Siegel type 4.

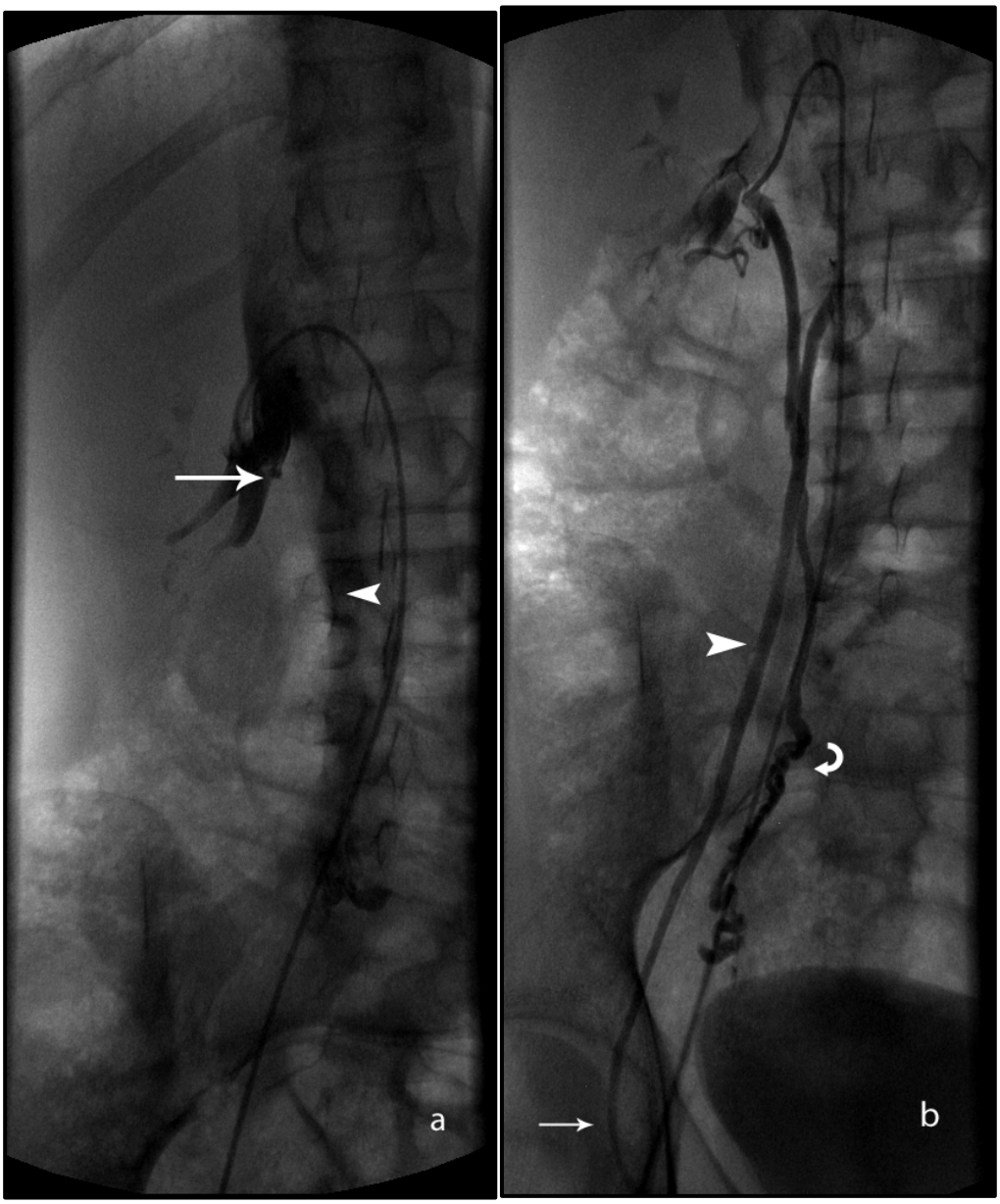


Fig 4: Insufficient ISV type 4a according Bähren (age: 29 years, left overt varicocele).
Fig 4a: Microcatheter injection after passing the outflow valve shows the V-shape of an additional competent valve (arrowhead).
Fig 4b: After crossing this second valve, a duplicated ISV (arrowhead) is seen as well as a partially filling renospermatic bypass (upper curved arrow). Lateral collateral (lower curved arrow) is visible.

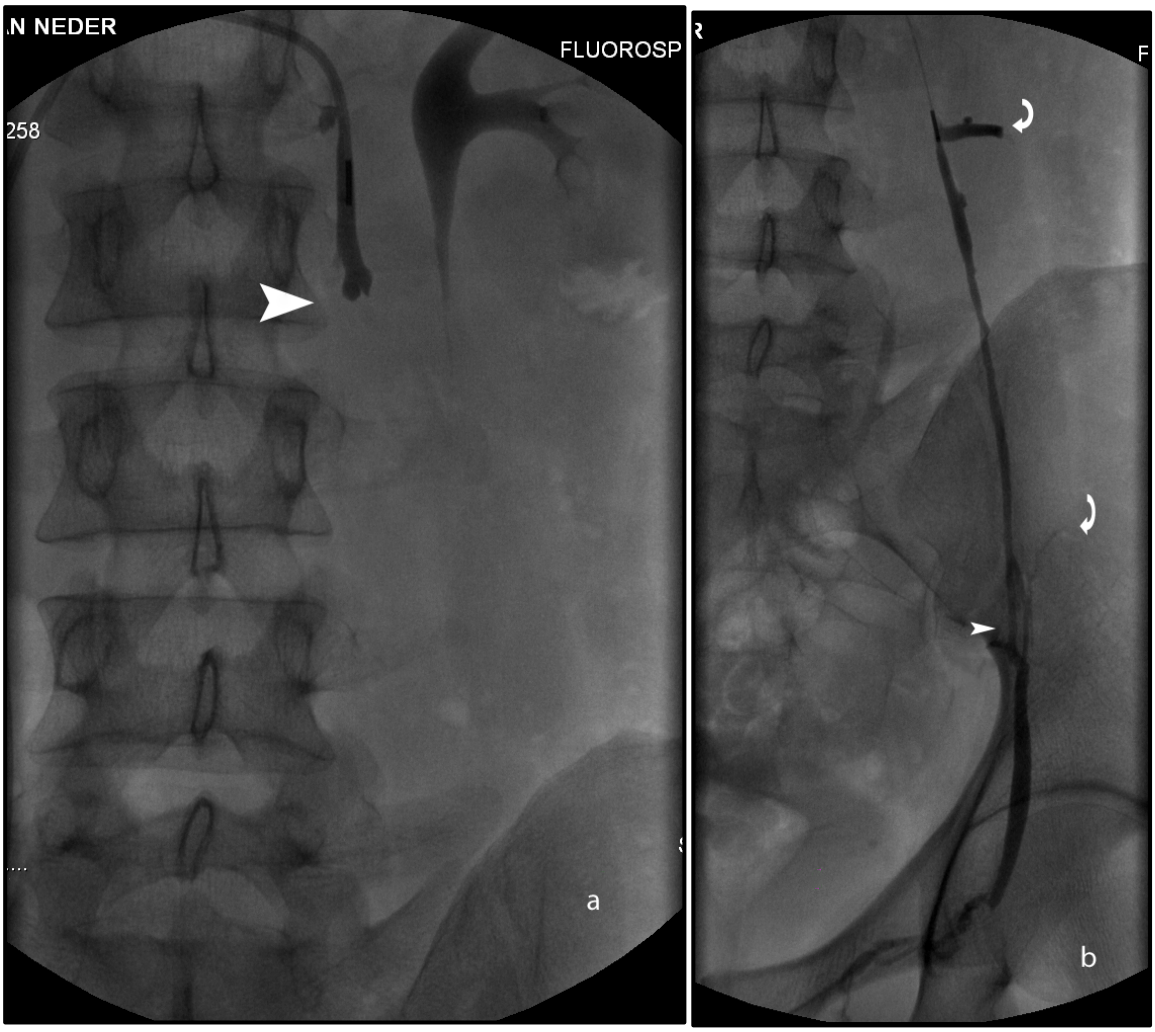
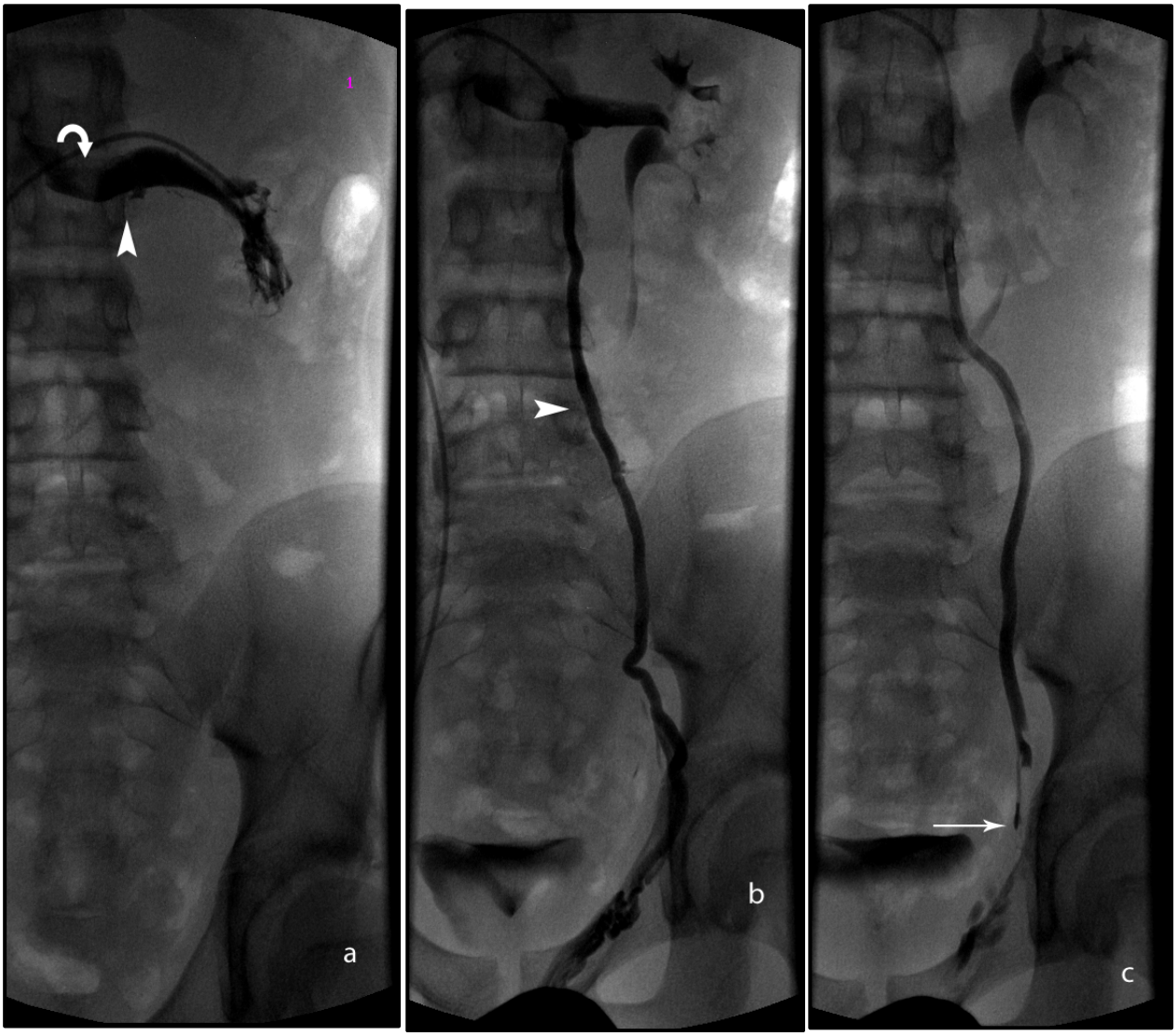


Fig 5: Insufficient ISV, which cannot be classified according Bähren (age: 25 years, left overt varicocele).
Fig 5a: Left RV phlebography with a competent outflow valve (arrowhead) and no spontaneous visualization of the ISV. Anterior nutcracker phenomenon (curved arrow) is visible.
Fig 5b: Selective phlebography after crossing the competent valve detected a solitary ISV insufficiency (arrowhead) without collaterals or bypasses.
Fig 5c: Microcatheter (arrow) phlebography at 0° position confirmed the solitary ISV without collaterals to explain the insufficiency.



METHODS AND MATERIALS

Patient selection criteria

Phlebographies of 497 consecutive varicocele embolizations (October 2004 - September 2010) were anonymized. Each patient was allocated a number (from 1 to 497) on a consecutive list with a link to his HIS (Hospital Identification system) number and the date of the phlebography. The first part of the HIS number consists of the date of birth. Arbitrarily, we excluded patients who were 17 years or older and younger than 25 years (N=63) to ensure groups that were distinctly adolescent or distinctly adult. Post hoc, patients with bilateral negative phlebography (N=13) were excluded as well as patients who were treated previously by open (N=5) or endovascular (N=1) surgery. We included 191 adolescents and 224 adults for a comparative study. This study was approved by the ethics committee of the hospital (EC: 2010/210).

Phlebography of the ISV

Phlebographies of the renal vein (RV) and the ISV were performed according standard techniques [14-15]. Venous insufficiency was substantiated by retrograde opacification of the spermatic vein and of the PP, either spontaneously or after passing a competent valve. Competent outflow valves were usually crossed with the diagnostic catheter, distal valves with a microcatheter. Bilateral phlebograms obtained with the 5 F.diagnostic catheter positioned in the RV and in the ISV (during 45° table inclination and Valsalva maneuver) and with the 3 F. microcatheter at 0° (without Valsalva maneuver) were used for study. Paraspermatic veins, connecting collaterals or renospermatic bypasses to the ISV were mapped as well as all visible and potentially important anatomical landmarks studied. A senior radiologist, expert in spermatic vein embolization, read the anonymized phlebographies.

Phlebographic characteristics.

1. *Spontaneous visualization of the ISV*

   Spontaneous visualization of the ISV is defined as opacification of the ISV (partially or completely) during RV or inferior caval vein (ICV) phlebography in anti-Trendelenburg position on a tilt table under Valsalva maneuver. Contrast medium might reflux either via an insufficient outflow valve (Fig 1a) or via a reno-spermatic bypass (Fig 2b).

2. *Incompetence of the outflow valve*

   The outflow valve was defined as incompetent whenever the cranial part of the ISV just below the RV was opacified during RV or ICV phlebography (Fig 1a).

3. *Outflow of the ISV in the RV*

   We defined the outflow of the left ISV as a "single " or as a "complex ". A complex outflow was defined when multiple connections between the ISV and the main RV existed. On the right side the outflow valve can be duplicated, with the second valve either at the ICV or the RV (Fig 3b). Complex outflows as defined for the left side do not exist at the right side.

4. *ISV insufficiency*

   ISV insufficiency was defined whenever contrast medium appeared in the PP, either after injection in the RV or after selective injection in the ISV (sometimes after passing competent valves) (Fig 1-5).

5. *Renospermatic bypass*

   A renospermatic bypass is a renal venous anastomosis directly connecting the ISV and the renal venous system, allowing reflux caudally from the outflow valve. This type of varicocele is also called " aberrantly fed varicocele "[16,2] (Fig 2b).

6. *Number of competent valves*

   We counted the number of competent valves below the outflow valve. A valve was considered competent whenever contrast-agent stagnated in the ISV building up a contrast column, caudally delineated by an inverted V-shape of the valve (Fig 4a). Competent valves on parallel or side branches were not counted if the PP was opacified by the main ISV branch.

7. *Duplication of the ISV*

   If a second vein paralleled the main ISV and both veins had a similar caliber, we considered this configuration as a duplication of the ISV [17]. Duplication can be complete or segmental (Fig 2d and 4b).

8. *Paraspermatic veins*

   Paraspermatic veins were defined as the small to very small veins running alongside the ISV, connecting to it on different levels and sometimes creating a fine network (Fig 1b). Paraspermatic veins are a phlebographic entity, which is neglected in literature but might be the cause of persisting opacification of the PP after embolization.

9. *Collaterals*

   We divided side branches in lateral and medial collaterals according to the direction of their course [18,17]. Medial collaterals were defined as branches connecting the ISV with the ICV, lumbar venous plexus and iliac veins or communicating with the opposite ISV (Fig 1b).Lateral collaterals were defined as branches connected to the iliac, retroperitoneal or colonic veins, except the reno-spermatic bypass (Fig 2b and 4b).

10. *Nutcracker phenomenon*

    The nutcracker syndrome results from the compression of the left renal vein between the abdominal aorta and the superior mesenteric artery (SMA) [19]. This "anterior" nutcracker might elevate the pressure in the ISV [20](Fig 5a). Compression caused by the SMA is reflected either by a contrast stagnation in the RV or by a small vertical band of higher contrast transparency. A "posterior" nutcracker exists when a retro aortic left RV is compressed between the abdominal aorta and the spine, which is seen as a broader vertical band of contrast transparency on the RV phlebography [21]. Finally, a mixed nutcracker consists of a double left RV (Bähren type 5, Fig 6) with one branch running anteriorly and one posteriorly to the abdominal aorta [22,23] (Fig 2a).

Fig 6: *Bähren classification (left ISV) [Bahren et al., 1992, Rofo, 157, 355-60] (with permission of Röfo,Thieme)*

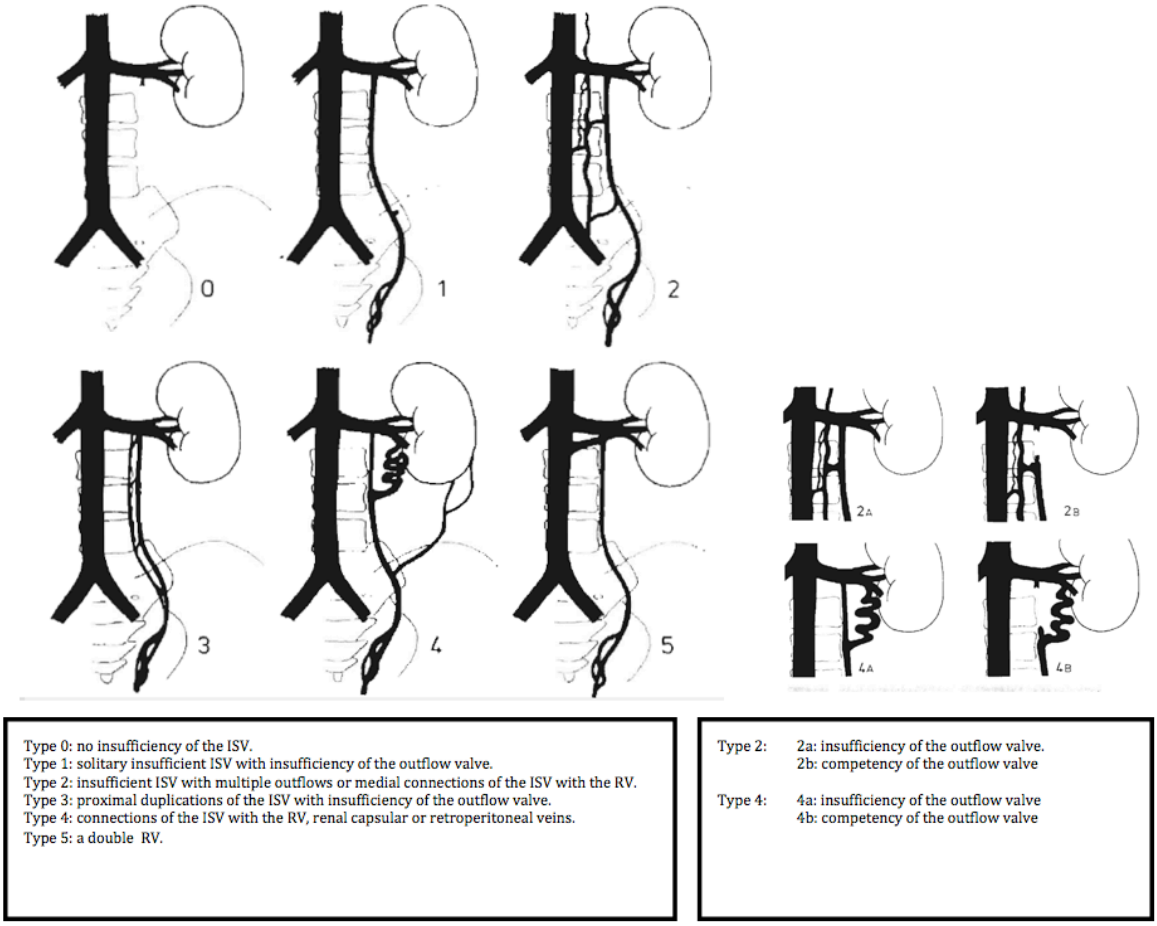
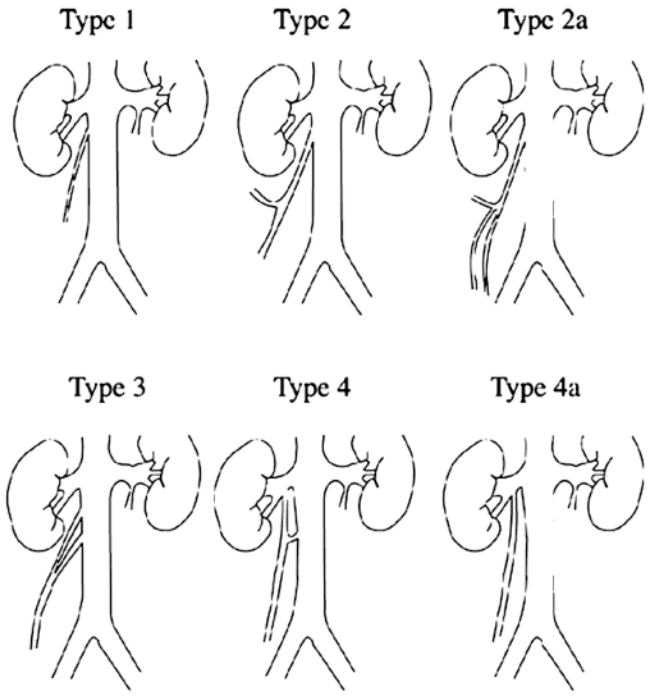


Fig 7: *Siegel classification (right ISV) [Siegel et al., 2006, Cardiovasc Intervent Radiol, 29, 192-7] (with permission of CVIR, Springer)*



Type 1: solitary ISV draining the inferior caval vein (ICV)
Type 2: ISV with a collateral vein to the lateral retroperitoneal system
Type 2a: ISV with a collateral vein to the lateral retroperitoneal system and 2 parallel veins to the inguinal canal
Type 3: ISV with two separate drainages in the ICV
Type 4: ISV with two separate drainages, one in the ICV and one in the RV
Type 4a: ISV draining in the RV

11. Diameter of the ISV

Calibrated measurement of the largest diameter of the ISV, opacified during Valsalva maneuver and tilted table position, was performed on the workstation (Fig 1a).

12. The outflow angle of the ISV

The inner angle between ISV and the RV on both sides or with the ICV on the right side was measured on the venogram performed during Valsalva maneuver and tilted table position (Fig 1a). In case of duplication (as in Siegel type 3 and 4, fig 7) both outflow angles were measured (Fig 3b) [24, 25].

13. Outflow level of the right ISV into the ICV

The outflow level of the right ISV to the ICV is determined by the level of the vertebral column. The outflow level can be linked to one vertebral body or to two consecutive vertebral bodies if the outflow is at the level of the intervertebral disc [26]. Both outflow levels were determined if the distal right ISV was duplicated (Siegel type 3).

14. ISV classification (Fig 6 and 7)

Bähren and Siegel classification were based on the venogram obtained after contrast injection in the RV or ISV under Valsalva and in anti-Trendelenburg position.Patients with a competent outflow valve and no ISV visualization (Bähren type 0) and indefinable cases (for example: Fig 5) were eliminated from statistical analysis. Siegel did not include the competency of the outflow valve in his classification (no type 0).

Statistical data processing.

Univariate analysis was performed with the SPSSv 20 statistical software, using the Chi-squared test for the categorical variables and the Mann-Whitney U-test for the numeric variables. A $P < 0.05$ was accepted for significant difference.

Table 1a: Phlebographic characteristics of the left insufficient ISV in adults and adolescents.

Phlebographic characteristics of the left ISV		**Adolescents** N= number adolescents/total N=191(%)*	**Adults** N=number adults/total N=218 (%)*	**P-value**
Spontaneous visualization of the ISV		164/190(86.3)	154/214(72.0)	0.001
Incompetence of the outflow valve **		128/190(67.4)	125/216(57.9)	0.052
Outflow of the ISV in the RV	Single outflow	179/191(93.7)	189/218(86.7)	0.021
	Complex outflow	12/191(6.3)	29/218(13.3)	
Reno-spermatic bypass	Absent	142/191(74.3)	175/218(80.3)	0.157
	Complete	49/191(25.7)	43/218(19.7)	
Mean nr. of competent valves below the outflow valve		0.17	0.33	0.000
Duplication of the ISV	Solitary ISV	130/191(68.1)	127/218(58.3)	0.052
	Multiple /duplication	61/191(31.9)	91/218(41.6)	
Paraspermatic veins		178/191(93.2)	204/218(93.6)	1.000
Collaterals	collaterals	108/191(56.5)	154/218(70.6)	0.030
	lateral collaterals	92/191(48.2)	128/218(58.7)	0.037
	medial collaterals	58/191(30.4)	97/218(44.5)	0.004
Nutcracker Phenomenon	Absent	120/157(76.4)	189/200(94.5)	0.000
	Anterior	14/157(8.9)	4/200(2)	
	Posterior	22/157(14)	6/200(3)	
	Combined	1/157(0.6)	1/200(0.5)	
Diameter of the ISV(mean) cm		4.00	3.96	0.378
Outflow angle of the ISV(mean)°		103.66	108.30	0.076
Outflow angle of the ISV if Bährens type 2(mean) °		110.00	106.46	0.885
Bähren classification**	Type 1	60/185(32.4)	51/209(24.4)	0.009
	Type 2	32/185(17.3)	36/209(17.2)	
	Type 2b	12/185(6.5)	38/209(18.2)	
	Type 3	20/185(10.8)	12/209(5.7)	
	Type 4a	11/185(5.9)	18/209(8.6)	
	Type 4b	45/185(24.3)	44/209(21.1)	
	Type 5	5/185(2.7)	10/209(4.8)	

* For some characteristics the number of patients does not equal the total number of adults or adolescents because we omitted patients in whom the characteristics could not be determined.
** The sum of type 2b and 4b is lower than the number of competent outflow valves, because the Bähren classification does not take into account insufficiencies that can only be proven by passing the competent outflow valve. Moreover 15 patients were excluded (9 adults and 6 adolescents) because their phlebography could not be classified according Bähren. Type 0 was encountered in 6 adults.

Table 1b: Phlebographic characteristics of the right insufficient ISV in adults and adolescents.

Phlebographic characteristics of the right ISV			**Adolescents** N= number adolescents/total N=28 (%)*	**Adults** N=number adults/total N=80(%)*	**P-value**
Spontaneous visualization of the ISV (IVC injection)			0/27(0.0)	5/77(6.5)	0.323
Spontaneous visualization of the ISV (RV injection)			4/27(14.8)	11/78(14.1)	1.000
Incompetence of the outflow valve (IVC injection)			1/26(3.8)	5/77(6.5)	1.000
Incompetence of the outflow valve (RV injection)			4/26(15.4)	10/71(14.1)	1.000
Reno-spermatic bypass		Absent	26/28(92.9)	78/80(97.5)	0.290
		Complete	2/28(7.1)	2/80(2.5)	
Mean nr. of competent valves below the outflow valve			0.11	0.23	0.514
Duplication of the ISV		Solitary ISV	12/28(42.9)	37/80(46.2)	0.304
		Multiple / duplication	16/28(47.2)	43/80(53.7)	
Paraspermatic veins			23/28(82.1)	71/80(88.8)	0.513
Collaterals	collaterals		13/28(46.4)	40/80(50)	0.744
	lateral collaterals		12/28(42.9)	34/80(42.5)	1.000
	medial collaterals		5/28(17.9)	28/80(35.4)	0.099
Outflow level of the ISV into the ICV		L1	0/28(0)	3/79(3.8)	0.964
		L1-L2	6/28(21.4)	17/79(21.5)	
		L2	10/28(35.7)	30/79(38)	
		L2-L3	9/28(32.1)	20/79(25.3)	
		L3	3/28(10.7)	8/79(10.1)	
		L3-L4	0/28(0)	1/79(1.3)	
Diameter of the ISV(mean) cm			3.51	3.99	0.023
Outflow angle of the ISV and the ICV (mean) °			31.04	25.13	0.070
Outflow angle of the ISV and RV (Siegel type 4a) (mean)°			110.60	90.83	0.383
Siegel classification		Type 1	9/28(32.1)	29/79(36.7)	0.532
		Type 2	8/28(28.6)	21/79(26.6)	
		Type 2a	6/28(21.4)	13/79(16.4)	
		Type 3	0/28(0)	5/79(6.3)	
		Type 4	1/28(3.6)	7/79(8.9)	
		Type 4a	4/28(14.3)	4/79(5.1)	

* For some characteristics the number of patients does not equal the total number of adults or adolescents because we omitted patients in whom the characteristics could not be determined.

Table 2: Comparison of the distribution of Bähren phlebographic types in previous studies with our series (2014)

	Bähren 1983	Sigmund 1987	Bähren 1992	Lenz 1996	Garel 2004	Wunsch 2004	Current study 2014 (Vanlangenhove)		
							All patients	Adolescent	Adults
N=patients	230	717	1081	416	65	5500	400	185	215
range / mean age in years	NA/NA	10-59/22.8	12-47/22	NA/29.5	9-17/NA	NA/NA	10-64/24.3	10-16/13.7	25-64/34
Type 0	NA	6%	1.5%	7.2%	0%	4,7%	1.5%	0%	2.8%
Type 1	40%	68.9%	46.4%	54.1%	57%	48.5%	27.8%	32.4%	23.7%
Type 2a	22%	5.2%	12%	4.3%	8%	11%	17%	17.3%	16.7%
Type 2b			2.9%			1.7%	12.5%	6.5%	17.7%
Type 3	21%	2.4%	11.7%	5.0%	3%	12.4%	8%	10.8%	5.6%
Type 4a	13%	8.9%	9.6%	7.7%	4.5%	10.5%	7.2%	5.9%	8.4%
Type 4b		7.0%	9.5%	17.5%	12%	8.4%	22.2%	24.3%	20.5%
Type 5	4%	1.7%	2.5%	4.1%	15.5%	2.8%	3.8%	2.8%	4.6%

NA: no data available

RESULTS

The adolescent group consisted of 191 patients with a mean age of 13.7 years (range 10-16 years). The adult group comprised 224 patients with a mean age of 33.5 years (range 25-64 years). All adolescents had an insufficiency of the left ISV (N=191/191; 100%). Six adults had no left-sided pathology (N=6/224; 2.7%) but were included for analysis because of a right-sided insufficiency. Table 1a summarizes the results for the left ISV. Spontaneous opacification of the ISV during contrast injection in the left RV, failed twice as often in adults than in adolescents (28.0% versus 13.7%). The mean number of sufficient valves under the outflow valve was N= 0.17 in adolescents (range N=0-5) and differed significantly (P<0.001) from the mean number in adults N=0.33 (range N=0-3). Collaterals (both lateral and medial) and lateral and medial collaterals separately were significantly more often present in adults than in adolescents (56.5% versus 70.6%, 58.7% versus 48.2% and 44.5% versus 30.4%, P=0.030, P= 0.037 and P=0.004). The outflow region of the ISV into the RV was significantly more complex in adults (13.3% versus 6.3%, P=0.0021). Adolescents showed a trend to have more often a solitary ISV (68.1% versus 58.3%, P=0.052) and an insufficient outflow valve (67.4% versus 57.9%, P=0.052) than in adults. Adolescents with a competent outflow valve had twice as much a renospermatic bypass than adults with a similar outflow (67.7% versus 34.0%). Adults and adolescents with a competent outflow valve but no renospermatic bypasses and collaterals, were rarely encountered (2.7% and 2.1%).

The Bähren classification was significantly different between adults and adolescents (P=0.009). Type 1 and type 3 reflecting the plain kind of varicocele (incompetent valve with single or duplicated ISV, no collaterals) is overrepresented in adolescents. Type 2b (competent outflow valve, medial collaterals) is obviously more often seen in adults.

When combining the anterior and posterior compression syndromes of the RV, we established the nutcracker phenomenon in N=37/157 (23.5%) of the adolescents and in N=11 /200 (5.5%) of the adults (P< 0.001).

All the other investigated landmarks were not significantly different.

Table 1b summarizes the results for the right ISV. Right phlebography revealed an insufficiency of the ISV 2.5 times more frequently in adults than in adolescents (N=80/224 (35.7%) versus N=28/191 (14.7%), P < 0.001). The number of insufficient outflow valves was in adults and in adolescents much lower than at the left side (mean 16.2% versus 62.3 %). The diameter of the ISV was significantly smaller in adolescents than in adults (mean of 3.51 mm versus 3.99 mm, P=0.023). In contrast to the left side, the Siegel classification was not significantly different. In both groups, ISV with a single outflow valve (type 1, 2 and 2a) represented 80% of the varicoceles.

Bilateral insufficiency was 2.4 times more frequent in adults than in adolescents (N=74/224 (33%) versus N=28/191, 14.7%, P<0.001).

DISCUSSION

This study detected radio-morphological differences in the venogram of the left insufficient ISV between adults and adolescents.

Firstly, valve dysfunction, expressed by the lower number of secondary competent valves and by the higher number of insufficient outflow valves, seems a more relevant cause of reflux in the ISV in adolescents. This finding explains why spontaneous visualization of the ISV was significantly more frequently observed in adolescents than in adults (86.3% versus 72%, P= 0.001). Our impression that embolization is less laborious in adolescents was not false as we had objectively less competent valves to be crossed. Moreover, adolescents have more often a single outflow (94% versus 87%, P=0.021) and a solitary ISV (68% versus 58%, P=0.052), which are two characteristics that facilitate catheterization. As almost half of the adults had a functional outflow valve and adults had twice as much competent secondary valves, blood has to find another way to reflux into the ISV. A plausible pathway would be through connections between the systemic venous circulation and the ISV. Indeed in a significant number of adults (70.6% versus 56.5% in adolescents, P= 0.030), such collaterals could be identified. The percentage of adults with phlebographically disclosed collaterals is twice as high as what we knew from previous studies, which included the Bähren classification (Type 2 + Type 4 ranging from 20-35%, Table 2). Our higher collateral detection rate was probably purely technical because we performed selective microcatheter phlebographies in supine 0° position allowing reflux into spermatico-systemic connections.

Secondly, the divergence of some phlebographic characteristics was also reflected in the Bähren classification. This classification encompasses most of the anatomic variations including the competency of the outflow valve, but was never used to differentiate adult from adolescent ISV insufficiency. Bähren used his classification in order to treat or not to treat a varicocele [(22)]. Competent outflow valves are only found in Bähren type 2b and 4b. The difference between adolescents and adults in our study was obvious in type 2b, but not in type 4b. In type 4b Bähren made no differentiation between renospermatic bypasses and lateral collaterals. Since the former is more often observed in children and the latter in adults, type 4b is equally spread over both groups. Types 1 and 3 (no visible collaterals on the venogram) were overrepresented in adolescents (43.2% versus 30.1% in adults), which is in agreement with the observation that collaterals are significantly more often seen on adult venograms.

Braedel et al proposed an ontogenetic etiology for idiopathic left varicocele that rejects the theories of missing valves and outflow obstruction (compression syndrome) [(2)]. The embryological development of the left ISV from the subcardinal veins is a complex process where all veins (ISV, adrenal veins and RV) have to converge into the single left RV (in contrast to the right side where the veins drains directly in the caval vein). Braedel argued that a poorer drainage ensued from these involuting veins. These veins remain open during embryogenesis to form a collateral draining network, which would correspond with the medial and lateral collaterals we observed on the phlebogram and, again according to Braedel, would be the major cause of the etiology of varicoceles. Indeed, our phlebographic study proved for the first time the high incidence of such collaterals. However if Braedel's theory would be true, shouldn't we have found an equivalent high number of collaterals in both adults and adolescents at the left side? As it was not the case, it seems that besides an ontogenetic cause other mechanisms play a role as well.

Thirdly, we found indications for congenital forms of varicoceles. One of them could be the renospermatic bypass. In agreement with other investigators we found 19.7% of adult left ISV to

be fed aberrantly by a renospermatic bypass [2,16]. This number of renospermatic bypasses explained only 45% of the adult insufficient ISV's in the presence of a competent outflow valve. In adolescents with a similar veno-architecture (N=62/190, 32.6%) a reno-spermatic bypass explained the insufficiency in 81% of the cases. Therefore the reno-spermatic bypass is probably a congenital form of the disease. Another type of congenital varicocele could be the nutcracker phenomenon, which we observed 4.2 times more often in adolescents (23.5%) than in adults (5.5%). In a congenital double left RV, compression syndromes such as the nutcracker phenomenon might cause chronic reflux. This type of circumferential RV corresponds with type 5 of Bähren. Garel et al. found 15.5% of varicoceles with type 5 in his group of only adolescents. Congruent with all other investigators (Table 2) we could not confirm this high number of type 5. Therefore the nutcracker seems to be a distinct cause of varicocele, where constitution and growth evoke a vascular anatomical conflict in the retroperitoneum.

In our study population, 28.3% of the patients had an insufficiency of the right ISV with a significant difference between adults (39.6%) and adolescents (15.6%). In the latter group the right varicocele was attributed to outflow valve dysfunction in only 17.8%. This percentage was equally low in adults (15%). We had no indications for a distinct valve disease, which would affect both the left and the right outflow valve in the same patient. Whether the right outflow valve was competent or not, left outflow valve insufficiency was present in 70%.

In view of the large group with functional primary valves, we expected that the role of systemic collaterals (eventually reno-spermatic bypasses) would be more pivotal at the right than at the left side. However, this was not confirmed by the reading. Although we found twice as much collaterals than Siegel did in his study, still 30% of the right varicoceles remained unexplained. The phlebographic technique cannot be accounted for it as it was the same technique as on the left side.

We applied the Siegel classification for the right-sided varicocele but we could not encounter a difference between adolescents and adults (Table 1b). In agreement with Siegel's classification (Type 2 +Type 2a) we found lateral collaterals in 42 % both in adults and in adolescents. On the contrary, medial connecting collaterals were two times more frequently encountered in adults (35.4% versus 17.9%). These medial collaterals are not considered in the classification of Siegel for unclear reasons. It seems that by aging, medial systemic collaterals develop and might be a cause of the extra number of varicoceles in adults. Also the wider diameter of the right ISV in adults might be an expression of a chronic reflux that already started in adolescence.

The 2.4 times higher incidence of bilateral varicoceles in adults can be attributed to the higher number of right-sided insufficiencies in adults. Unilateral right varicocele is very rare and should always be an indication to exclude a situs inversus and renal or retroperitoneal masses [27-29].

Our phlebographic reading study had some limitations. Firstly, the delineation of adults versus adolescents was somewhat arbitrary and created two groups with different age pattern. The adolescent group was compact and homogenous consisting of 6 life years, whereas the adult group was widely spread over 41 life years. Moreover as we excluded the age group between 17 and 25 years, we could have missed landmarks, which first appeared in this group or which changed gradually and continuously with age. Analysis comparing each life year to find trends and evolutions in phlebographic landmarks would require a much larger study population particularly in the adult group.

Secondly, we did not analyze anatomical characteristics in respect of clinical presentation because we thought that symptomatic varicoceles (local discomfort, infertility) were usually related with

adult age and asymptomatic varicoceles with adolescent age. On the other hand it could be issue of further study to find out whether within the age groups, the severity of varicocele (expressed by the clinical grade 1 to 3 and the color doppler grade 1 to 4) is associated with specific landmarks or subgroups of varicoceles [30, 31].

Thirdly, although we found a higher incidence of collaterals than in other reports, we do not know how and where these collaterals were connected with the systemic venous circulation. A proof of flow reversal in these collaterals, hence disclosing the pathway of reflux cannot be provided by standard or even selective supine venography. Retrograde catheterization of these collaterals could provide an answer, but this is in the routine of embolization not practical. Still there are cases in both groups with a competent outflow valve but without any phlebographic hint explaining the reflux.

Although some landmarks were significantly more often observed in one of the groups, none of the anatomical characteristics could be exclusively linked to adults or adolescents. However, the age related distribution of particular landmarks could give a clue to unravel the complex pathophysiology of varicoceles.

The higher incidence of valve dysfunction, the renospermatic bypass and the nutcracker phenomenon in adolescents, are arguments against a pure evolutive disease of the left varicocele. On the right side landmarks were found that pointed at a progressive reflux resulting in an increasing incidence of right-sided varicoceles in adults.

Spermatico-systemic collaterals seem to play a pivotal role in the development of varicoceles. It remains to be determined whether all types of varicoceles will lead to testicle hypotrophy and infertility. It might be that varicoceles with specific phlebographic landmarks are only a congenital form of the normal. The concept of varicocele as a congenital anomaly should open our thinking towards a concept of testicular dysplasia. Indeed the congenital anomaly of the venous drainage system could be just a sign of a more complex embryopathogenetic process similar as it is in cryptorchidism. Which could also explain the testicular atrophy that is observed. The only way to proof this concept would be by taking biopsies in so-called congenital and non-congenital conditions and compare these.

CONCLUSION

Although no clear-cut veno-anatomical base was found to distinct adult from adolescent varicoceles, some characteristics point at congenital forms of left varicoceles in adolescents (reno-spermatic bypass, "nutcracker" and probably valve pathology). In adults, reflux is likely to be induced via collateral pathways. For right ISV insufficiency, we found indications that the adult varicocele might be a late stage form of the adolescent varicocele. Whether these phlebographic characteristics could alter the indication of preventive treatment, particularly in adolescents, could be subject of future study.

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Preface to part 2.2

Today, the association between varicocele and infertility is explained by the combination of lifestyle, genetic factors and the effects of reflux of blood into the PP.

The reflux of blood is caused by insufficient valves, which we can observe during phlebography. This blood reflux not only ensues an increased temperature around the testicle, but would also cause a rise of the hydrostatic pressure in erect position.

The increased pressure may cause additional temperature increase since the cooling system of the testicle namely the PP, is draining less efficiently the blood by this counter-pressure. Toxic degradation products in the testis cannot be disposed and cause local harm. Moreover, increased pressure can interfere with the arterial and nutritional supply of the testicle and decrease spermatogenesis and testicle growth.

In an editorial of Andrologia, Gat titled " Erect posture of humans leads to infertility. " [(1)]. In 2 other articles, he describes that increased pressure at the PP is only caused by the height of the blood column in the insufficient ISV (distance between PP and renal vein) and that this pressure is high enough to cause testicular insufficiency and infertility in varicoceles. So far "the theory".

Pressure measurements in the PP or inguinal ISV of varicocele patients were previously done by direct measurements through a needle or catheter into the PP [(2-4)]. We consider the methods used in the past and the obtained results inconsistent and unreliable.
Interested in the concept, but rather critical, we started a study with the aim to measure directly pressures in the caudal ISV (aim 9) and to find out whether infertility can be explained by the principle of elevated hydrostatic pressure (aim 2&10).

Our idea to perform pressure measurements in the ISV was initially difficult to execute due to the lack of a standardized method. In the end, we developed a set-up with an external pressure transducer set whereby the pressure at the tip of the microcatheter could be compared with two different commercial pressure wires (aim 9). Pressure wires have a transducer on the wire and measure independently to table movements. The set-up was tested in vitro (in an experimental tube) and in vivo (endovascularly in the ISV) and proved to be reliable.
Pressure measurements in the human ISV were performed in the supine 0° and semi-erect 45° position, in the renal vein and the ISV. The obtained pressures were compared with the extrapolated pressures calculated from the distance of the PP to the renal vein (the “height” of the fluid column in the ISV). This last calculated pressure reflects the hydrostatic pressure as formulated by Gat et al.

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4. 2.2 Internal spermatic vein pressure measurements in varicoceles: does erect posture in varicoceles lead to infertility?

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ABSTRACT

PURPOSE:

To determine the hydrostatic pressure and to explore the fluid dynamics in the internal spermatic vein in standing patients with varicocele.

METHODS AND MATERIALS:

Methodological conformity of pressure measurements was tested by comparing theoretical calculations with in vitro measurements using pressure wires and microcatheters. In 42 varicocele patients, hydrostatic pressure was calculated from the conversion of the distance between the renal vein and the inguinal internal spermatic vein (height of a static fluid column). Direct in-vivo pressure measurements were performed in the inguinal segment of the internal spermatic vein in supine and semi-erect 45° position. Simultaneously, systemic venous pressure was registered in the left renal vein. Pressure values in an erect 90° position were obtained by extrapolation from the measured pressure results in the 45° position.

RESULTS:

Theoretical pressure calculations and in-vitro pressure measurements were compatible. The mean height of the renal vein was 26.3 cm, corresponding with a hydrostatic pressure of 20.3 mm Hg. At the inguinal internal spermatic vein, the mean pressure increased from 15 to 23.5 mm Hg when tilting the table from 0° to 45° upwards. Extrapolation to an erect 90° position, the mean hydrostatic pressure becomes 33.2 mm Hg. The mean systemic venous pressure, as objectified by measurements in the renal vein, varied between 12 and 10 mm Hg in 45° and 0° supine position respectively. The difference of 12.9 mm Hg between the mean pressures obtained by the two methods reflect the in-vivo systemic venous pressure.

CONCLUSION:

The hydrostatic pressure in the spermatic vein in a standing man with a varicocele is at least 20 mm Hg. Adding the omnipresent systemic 12 mm Hg venous pressure, the absolute intravenous pressure seems high enough to act as a counter pressure that could impair arterial supply and spermatogenesis.

KEYWORDS: varicocele –pressure - internal spermatic vein – pathophysiology

INTRODUCTION:

How varicoceles induce infertility is still unraveled and probably multifactorial. Experimental animal and clinical human studies revealed as pathophysiological mechanisms amongst renal and adrenal reflux [1-5], hormonal dysfunction [6,7], autoimmunity [8,9], scrotal and intratesticular hyperthermia [10,11], acrosane reaction defects [12], oxidative stress [13] also testicular blood flow alterations [10,14,15].

The capillary exchange pressure in the testis is very low and highly sensitive to alterations in the venous pressure [16]. In erect position, hydrostatic pressure at the level of the pampiniform plexus (PP) would be elevated in insufficient spermatic veins. This venous counter pressure could result in an inefficient nutrient supply and increased lymphatic wash out of key testicular hormones [17]. Important hormones for spermatogenesis have to be transported from one place to another in the testis or have to be passed out of the circulation. The effectiveness of this transport is strongly associated with the hydrostatic pressure in the testicle and the nutritional supply of the hormones by arterial inflow. An increase in hydrostatic pressure causes an impaired arterial supply that leads to a persistent hypoperfusion, hypoxia and stasis of blood in the testicle. Important hormones can not be delivered or transported and are washed out by the lymphatic drainage. This concept of hydrostatic pressure elevation was theoretically elaborated by other investigators, culminating in the claim that erect posture of men leads to infertility [18]. The hydrostatic pressure at the PP would be directly related to the height of the overlying blood column, which is the distance between the PP and the renal vein (RV). This could result in a pressure of 27 mm Hg at the right side (height of 35 cm) and 31 mm Hg at the longer left side (height of 40 cm)[19]. This theoretical prediction of hydrostatic pressure in an insufficient internal spermatic vein (ISV) seems not in accordance with older clinical experiments [20, 21]. Since then, no attempts have been made to prove the thesis of hydrostatic pressure by clinical data.

Assessment of hydrostatic pressure in a venous system can be performed by two approaches, of which the calculation from the height of the fluid column (distance between the RV and PP) can be counterchecked by a direct intravenous pressure registration. For this purpose, we developed a standardized method for venous pressure measurements through a 3 Fr. microcatheter, which was first evaluated in vitro and then in vivo. Then, we recruited varicocele patients referred for spermatic vein embolization to perform in vivo distance and pressure measurements.

Fig 1: Hydrostatic pressure in a closed fluid filled tube: the experimental set-up.
Hydrostatic Pressure = $\rho \, x \, h \, x \, g$ Pascal with 1mm Hg = 133.322 Pascal or
P (mm Hg) = $\rho \, x \, h \, x \, g$ = (999 x ((sin α x C)+(cos α x r)) x 9.81) / 133.322) with
ρ = Density (for water or blood = 999 or 1050 kg/m^3 respectively) and
h = height of the fluid column (m); h (0°) = r; h (90°) = C; h (between 5°-85°) = height of the fluid column (A) + height inside the column (b)
Both heights A and b vary with the angle α of inclination according the formula (A=sin α x C) and the formula (b=cos α x r)
g = gravitational acceleration (9.81 m2/s)

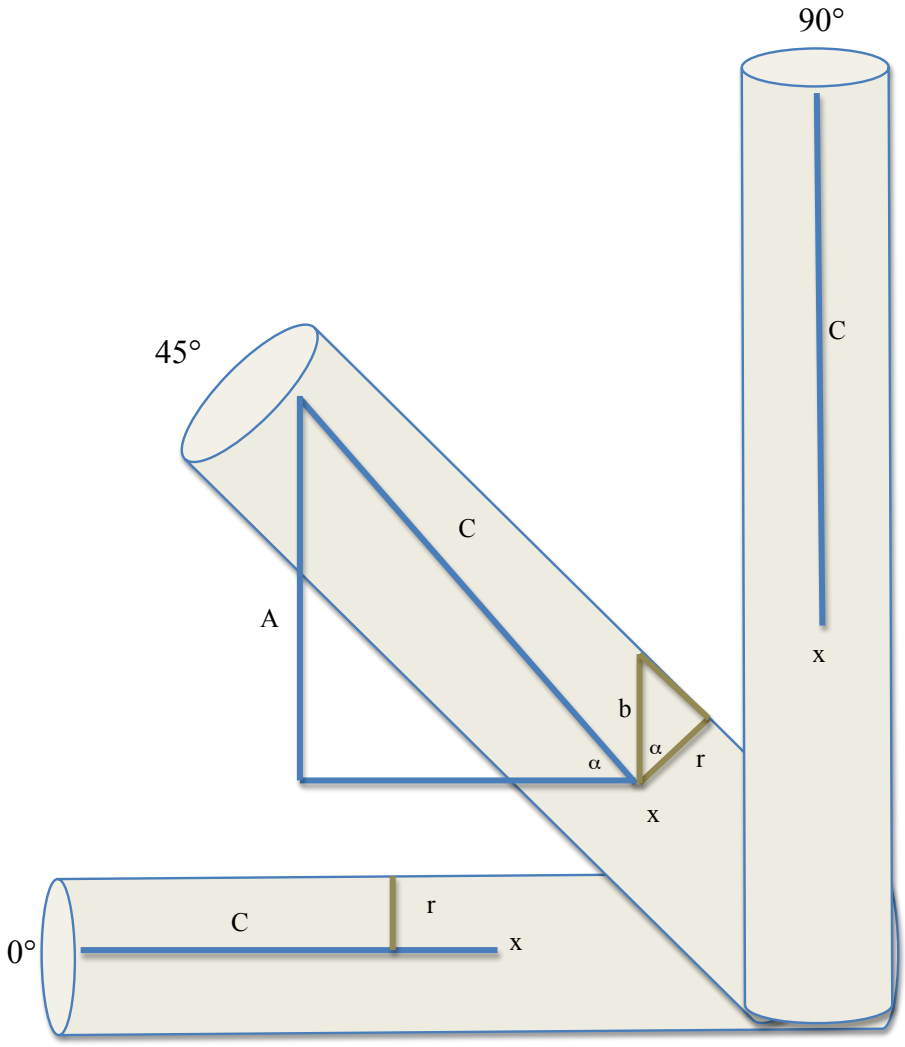
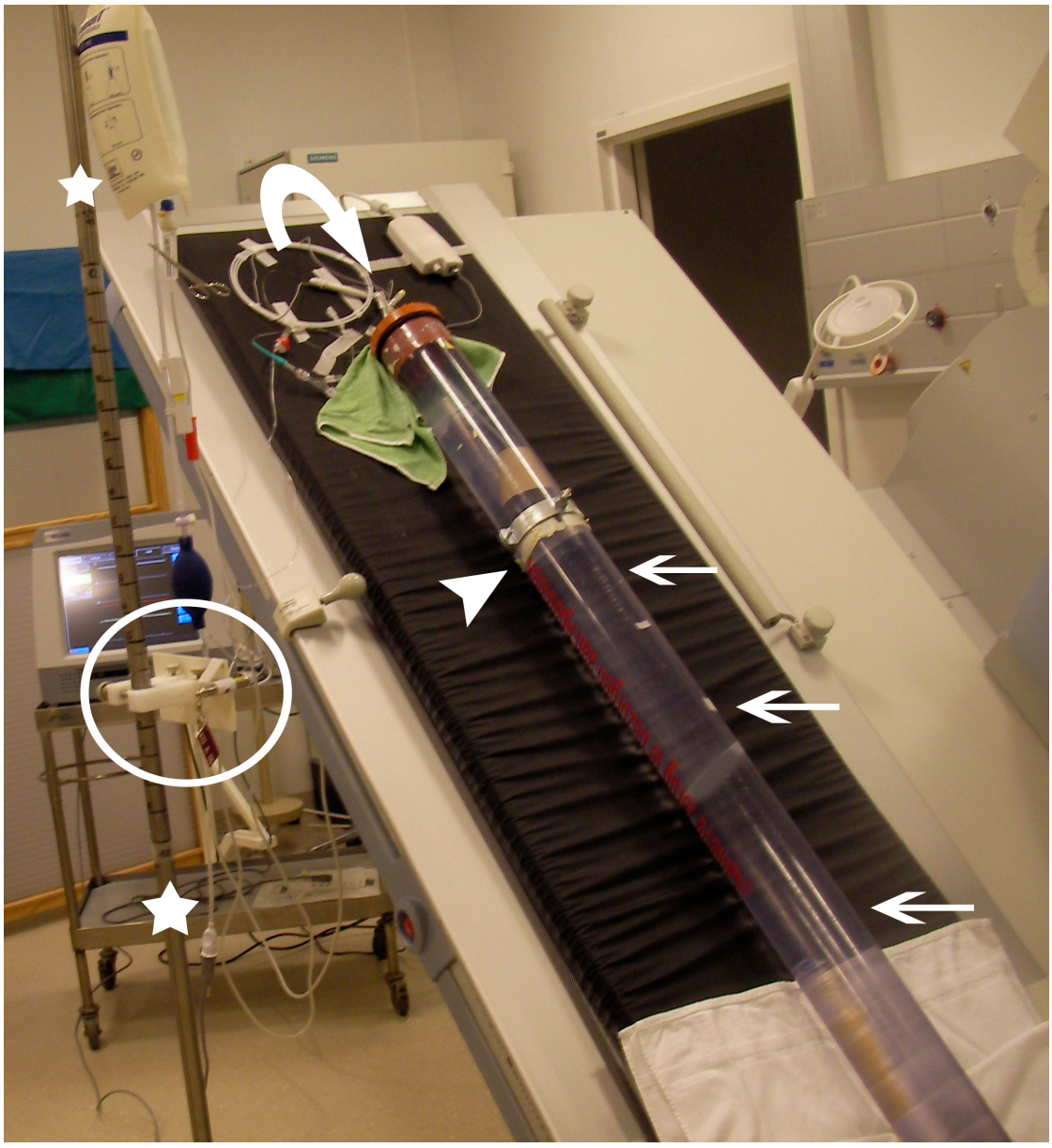
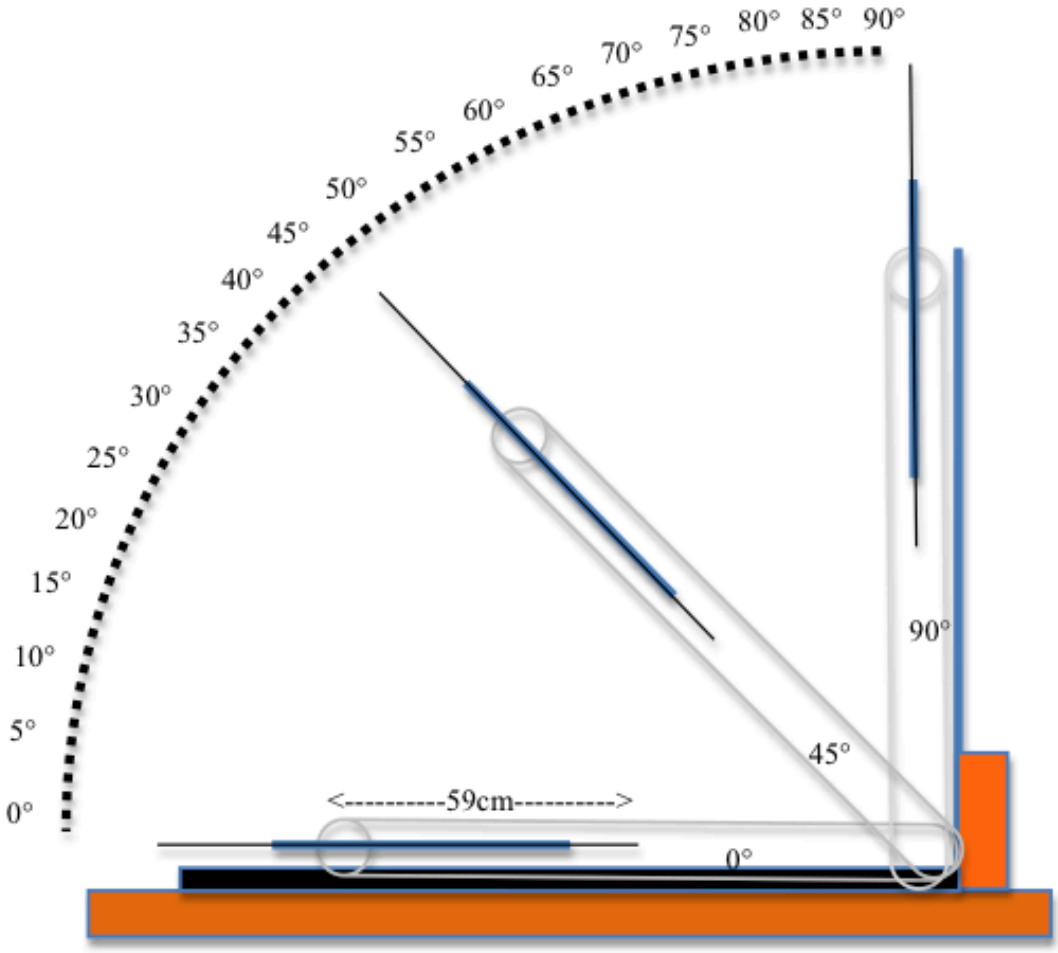


Fig 2: The experimental set-up with the plastic tube.

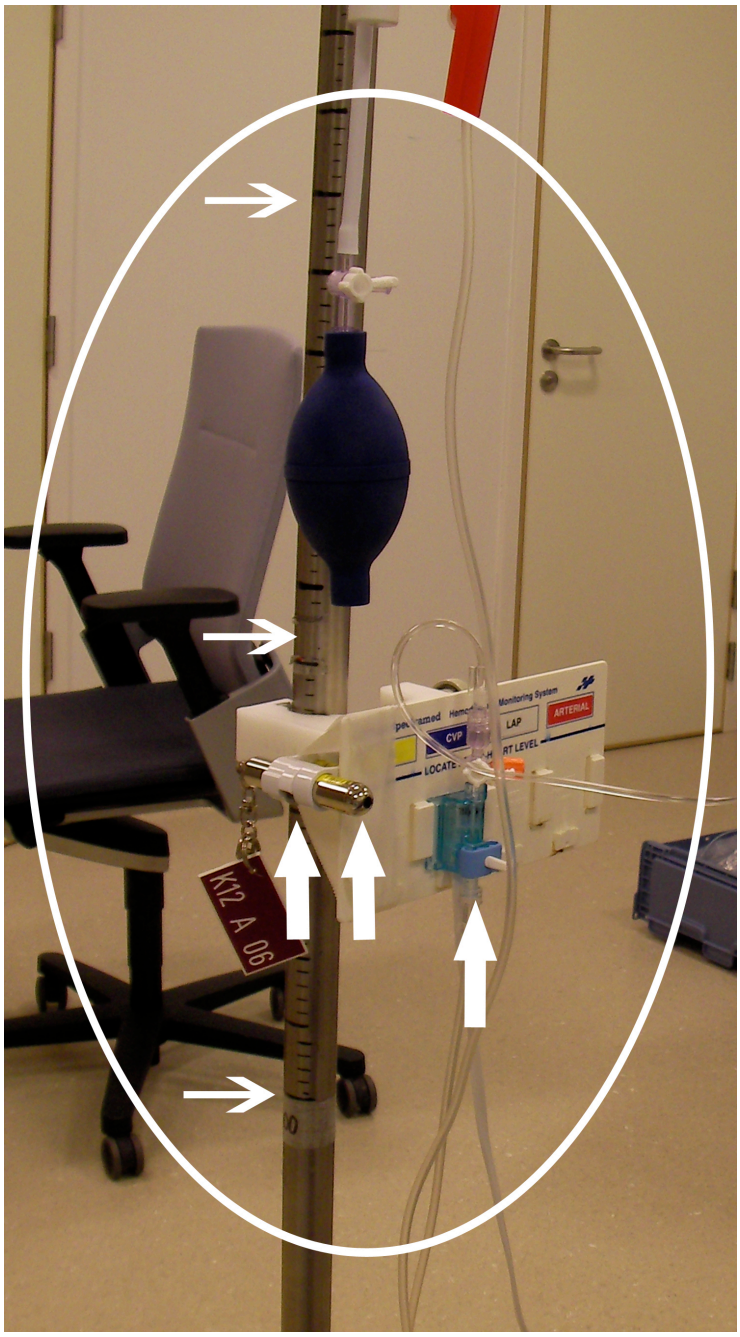
The plastic tube (arrows) filled with H_2O and fixed on an Iconos R 200 tilt table (Siemens, Erlangen, Germany). A multi perforated polyurethane disc with a small central hole (arrowhead) was placed into the tube at 50 cm, to keep the measurement system in the center of the fluid column. A 6 Fr. sheath (Terumo Europe, Heverlee, Belgium) was pierced through the screw cap of the tube (curved arrow). A 6 Fr. Cobra catheter (C2, Cook Europe, Bjaeverskov, Denmark), which was also used for spermatic vein embolization, was then introduced through the central hole of the disc. The laser light at the level of the pressure transducer (circle), fixed on the scaled infusion holder (star). Circle: detailed in the appendix



Supplemental 1 to Fig 2: Experimental set-up simulation with tube tilting of 5°.



Supplemental 2 to Fig 2: Detail of the infusion holder and pressure transducer system.
To facilitate correction for the height of the microcatheter tip, we used a radio-opaque yardstick in cm, which was fixed on the tilt table under the mattress, on the left side parallel with the patient (Fig 3). The position of the microcatheter could be read under fluoroscopy on the yardstick and was then transferred to a movable infusion holder. The scale on the infusion holder (small arrows) corresponded with the scale on the yardstick, already taking into account the thickness of the mattress (Fig 2) and the position of the ISV in the body with the use of a laser light (double arrows). The pressure transducer (arrow) system was then moved on the holder to the corresponding height for correct pressure measurements (Fig 2).



MATERIAL AND METHODS

Theoretical background of hydrostatic pressure.

Hydrostatic pressure in a closed fluid filled tube is determined and described by the formula $P = \rho \; x \; g \; x \; h$ (Fig 1). The ISV can be considered as a tube filled with blood. In a physiological state, competent valves would control the hydrostatic pressure. The fluid column is segmented and the maximum pressure would be determined by the height between two competent valves. In a pathological state, all valves might be insufficient and the hydrostatic pressure would then increase according to the height of the blood column.

Theoretical model

Theoretical calculations of hydrostatic pressure were based on a closed vessel model with a radius of 5 cm (r), filled with H2O. Pressures were calculated at a random chosen level of 59 cm (C) underneath the water surface, simulating the experimental set-up and for each 5° interval starting from a 0° horizontal up to a 90° up-right position, using the formula $P = \rho \; x \; h \; x \; g$ (Fig 1). In this formula the height h is composed of the height of the total fluid column (A or C) and the height of the fluid column inside the tube (b or r). The theoretical pressure can then be calculated for each inclination by the composed formula: $P=(999 \; x \; ((\sin \alpha \; x \; C)+(\cos \alpha \; x \; r)) \; x \; 9.81) \; / \; 133.322)$, where P is expressed as mmHg (1 mm Hg =133.322 Pascal) (Fig 1).

In vitro pressure measurements

To test the hydrostatic model and to evaluate the devices to be used for in vivo measurements, we set up the following experiment. A closed transparent plastic tube with a radius of 5 cm (according the theoretical model) and a random height of 155 cm was filled with water at body temperature (Fig 2). A 3 Fr. hydrophilic microcatheter (Microferret, Cook Europe, Bjaeverskov, Denmark) was coaxially pushed to a depth of 59 cm into the fluid tube and moved gradually from 0° to 90° with 5° interval (Fig 1). At each interval, pressure measurements were performed through the microcatheter and with two different pressure wires (PrimeWire™, Volcano Therapeutics, Rancho Cordova, USA; PressureWire®Certus, St. Jude Medical, St. Paul, USA). To check if correct pressures are measured with the microcatheter, pressures were also measured with the disposable pressure set (DTX Plus™ Disposable Pressure Transducer Sets, The Hague, the Netherlands)(Fig 2 + appendix 2). This transducer was kept at the same height of the tip of the microcatheter by means of a laser light (Fig 2). Pressure wires have a transducer on the wire and measure independently to table movements.

For each of the measure devices the experiment was repeated three times. Mean pressure and standard deviations were then compared with theoretically calculated pressures.

In vivo pressure measurements

Pressure wire versus the microcatheter (N=10)

Fig 3: Locations of venous pressure measurements.

Pressure measurements performed in the renal vein (small arrow), in the outflow (double small arrows) and inguinal segment (triple small arrows) of the internal spermatic vein in 0° and 45° position. Radio-opaque yardstick (curved arrow).

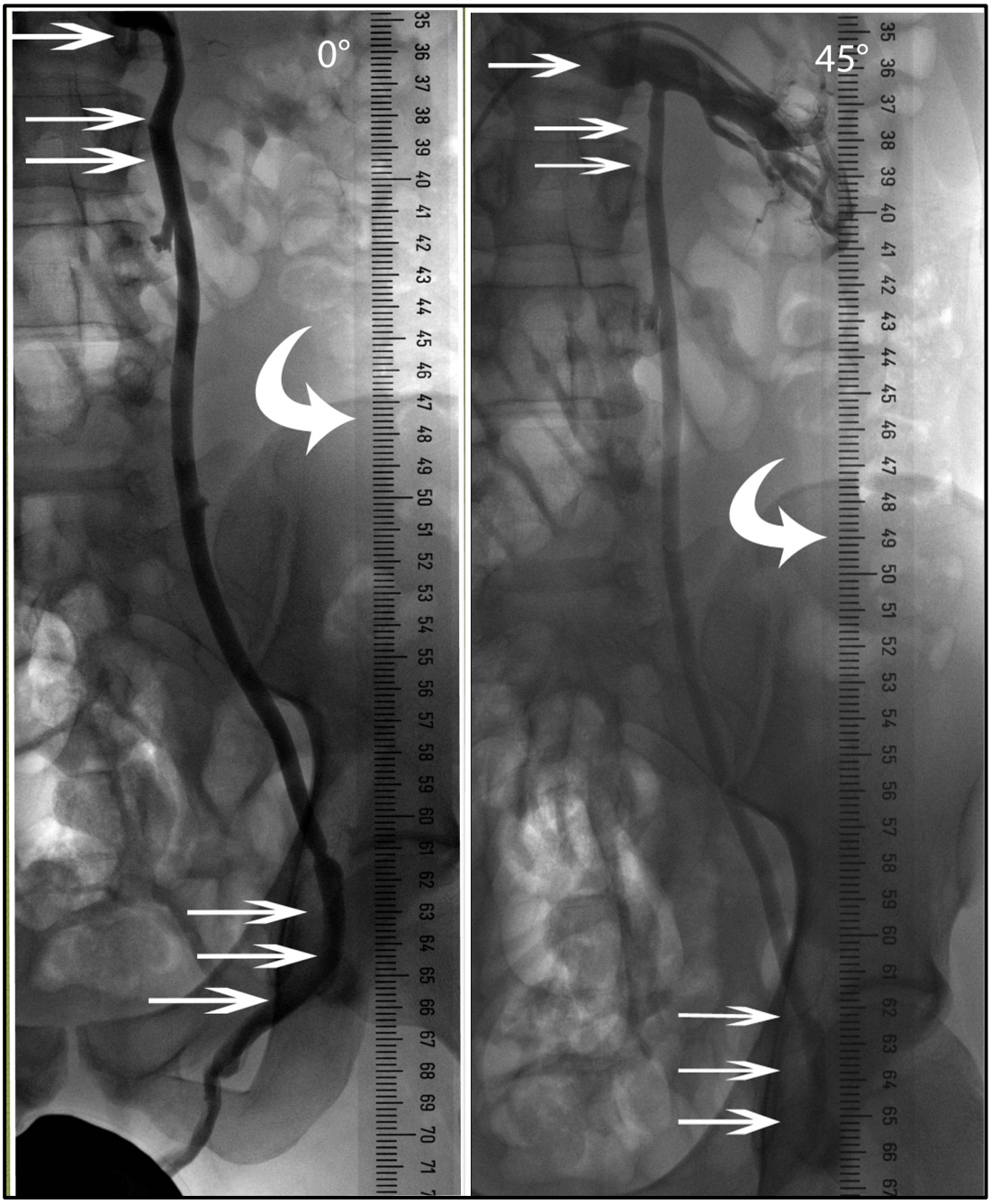
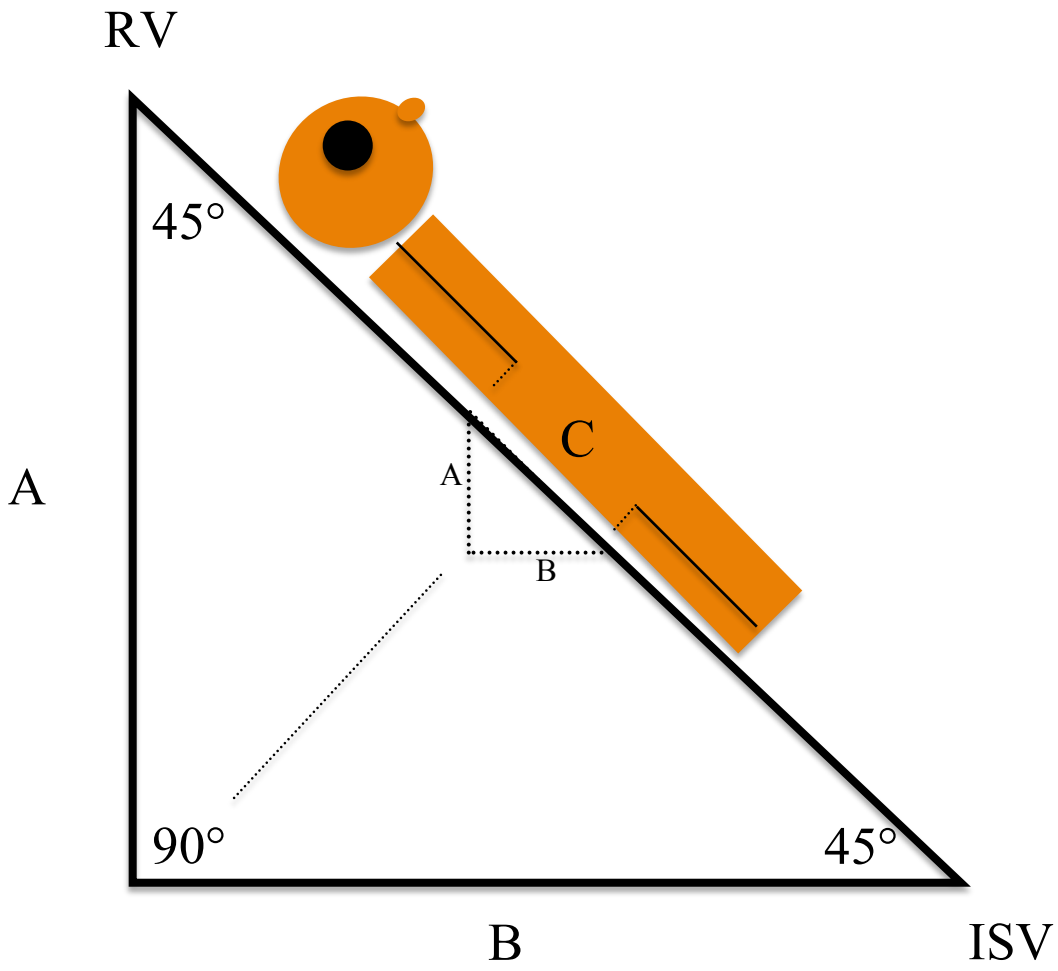


Fig 4: Extrapolation of 45° to 90 °: (RV= renal vein / ISV= internal spermatic vein)

The pressure P at 45° was calculated as $h = P / \rho \times g$ to obtain the height of the corresponding fluid column (A). This height (A) corresponds to the pendicular side of a triangle, of which the oblique side (C) would correspond to the theoretical height in 90° erect position. This oblique side (C) can be calculated with the formula: *sin 45°= obtained height / oblique side*. Then the oblique side was put in the formula $P = \rho \times g \times h$ to calculate the extrapolated pressure at 90° erect position.



Supplemental to Fig 4: Calculations of the extrapolated pressure.

$P = \rho \times h \times g$ P at 45° = 23.5 mmHg
h (height at 45°) = P *at 45°* / $\rho \times g$ = A = 23.5 mmHg/ (1050 kg/m^3 x 9,81 m/s² / 133.322 Pa) = 0.304 m
Sin 45° = A/C => C=A / Sin 45 ° = height at 90°= 30.4 cm/ 0.707107= 0.429 m
P *at 90°* = $C \times \rho \times g$ = 42.9 x (1050 kg/m^3 x 9,81 m/s² / 133.322 Pa) = 33.2 mmHg

Patients referred for embolization of a varicocele were invited to participate in our study (ethical committee 2012/318) of ISV pressure measurements. Patients were eligible for comparative pressure measurements whenever the phlebography showed an anatomy favorable for distal microcatheterization (incompetent valves). Ten patients were investigated with a pressure wire (N=5 with SJM, N=5 with Volcano) and a microcatheter simultaneously. In this way we obtained an in vivo comparison and a quality control of the measurement techniques. For financial reasons, we performed pressure measurements in the RV and the ISV in another 32 patients through the microcatheter alone. In those 32 patients, no anatomical restrictions concerning valve competence or bypasses were applied to avoid a selection bias.

Pressure measurements in the RV and ISV (Fig 3)

Right transfemoral phlebographies of the RV and the ISV were performed using 6 Fr diagnostic catheters in an anti-Trendelenburg position on the same Iconos R 200 tilt table (Siemens, Erlangen, Germany) under Valsalva maneuver with non-ionic isotonic contrast-agent (Visipaque 270 mgI/ml, GE Healthcare, Wemmel, Belgium). Venous insufficiency was substantiated by retrograde opacification of the spermatic vein and the PP. The diagnostic catheter and the 3 Fr coaxially hydrophilic microcatheter were positioned first in the horizontal part of the RV and then in the outflow of the ISV. Venous pressure was measured with the microcatheter and the reintroduced pressure wire in a 0° horizontal position and after 45° table inclination. This procedure was repeated after the microcatheter was advanced into the inguinal ISV, just above the PP. The PP itself was not aimed at for radiation exposure reasons (testis are lead-shielded in varicocele embolization). Positioning of the pressure transducer is crucial for obtaining correct values [(22)]. The transducer must be horizontally aligned with the tip of the microcatheter in the vein. We developed a technique that facilitate correction for the height of the microcatheter tip during table tilting (Fig 2 + appendix 2, Fig 3)

In vivo extrapolation from 45° semi-erect position to 90° erect position.

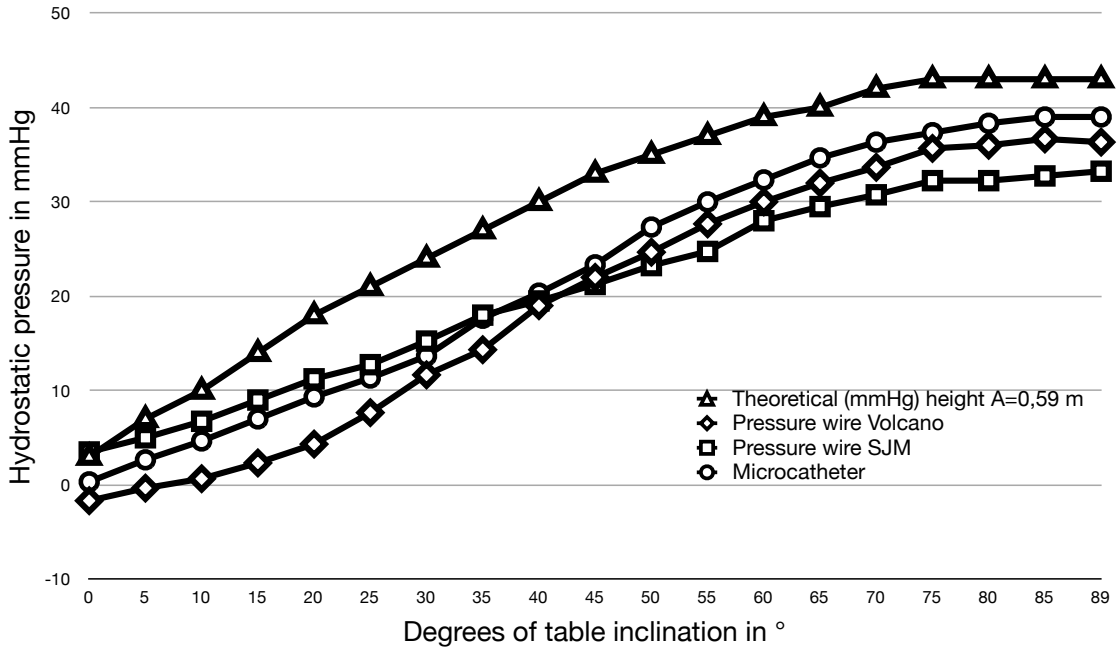
Pressure measurements during an erect position at 90° are difficult to achieve in aseptic conditions. Moreover orthostatic side effects might interfere with the performance and the results. Therefore we used the practical semi-erect position (45°) propagated by Mali et al. [(23)]. The pressures obtained in the semi-erect position were extrapolated to 90° position according the formula we used in the theoretical calculation (Fig 4). The obtained extrapolations in mm Hg were double checked with the theoretical pressure increase from 45° to 90 °.

In vivo distance measurements.

The radio-opaque yardstick fixed on the table along the patient, was used to measure the distance between the tip of the microcatheter in the inguinal ISV and the RV. We used this height to calculate the hydrostatic pressures in an erect position. We omitted the height of the fluid column inside the vessel (height b on Fig 1) because the radius of the ISV is only a few mm. Moreover, in an erect position the component height b becomes zero. These pressures were compared with the extrapolated pressures for a 90° erect position, as described in the previous paragraph. For each

patient, measurements were individually calculated and extrapolated. Then, means and standard deviations for the whole group of patients were used for comparison and interpretation.

Fig 5: Comparison of the pressures obtained in the theoretical model with the pressures registered in vitro with pressure wires and with the microcatheter.



Supplemental to Fig 5: Theoretical pressures compared with pressure wire and microcatheter measurements.

Theoretical pressures (mm Hg) in an experimental tube with 59 cm H_2O column (range 0°- 89°) compared with pressure wire and microcatheter measurements (mean mm Hg and SD)

Degree	Theoretical (mmHg) a=0,59	Pressure Wire				Microcatheter	
		Pressure wire Volcano		Pressure wire SJM			
		mean*	SD	mean*	SD	mean*	SD
0	3	-1.7	2.5	3.5	5.7	0.3	1.2
5	7	-0.3	2.5	5.0	4.7	2.7	2.5
10	10	0.7	2.1	6.8	3.9	4.7	1.2
15	14	2.3	2.5	9.0	2.7	7.0	1.0
20	18	4.3	3.5	11.3	1.0	9.3	1.2
25	21	7.7	2.5	12.8	0.5	11.3	1.5
30	24	11.7	0.6	15.3	1.0	13.7	2.3
35	27	14.3	1.5	18.0	0.8	17.7	0.6
40	30	19.0	1.7	19,5	1.0	20.3	2.1
45	33	22.0	1.7	22.0	1.5	23.3	2.9
50	35	24.7	1.5	23.3	1.5	27.3	0.6
55	37	27.7	1.5	24.8	1.7	30.0	1.0
60	39	30.0	1.7	28,0	1.4	32.3	0.6
65	40	32.0	1.7	29.5	1.9	34.7	1.2
70	42	33.7	1.5	30.8	2.1	36.3	1.5
75	43	35.7	1.5	32.3	2.2	37.3	2.1
80	43	36.0	1.0	32.3	2.2	38.3	2.1
85	43	36.7	1.2	32.8	2.2	39.0	1.7
89	43	36.3	1.5	33.3	2.2	39.0	2.6

* 3 different measurements

RESULTS

Theoretical calculation

A nearly constant pressure increase of 3 mm Hg was theoretically calculated for each 5° elevation of the table between 0° and 45° reaching a pressure of 33 mm Hg. From 50° to 70° the increase in pressure was 2 mm Hg per 5° and from 75° the pressure stagnated at a level of 43 mm Hg (Fig 5 + appendix 4).

In vitro pressure measurements: pressure wires versus microcatheter

Mean pressure measurements in the water tube at 45° were 22 mm Hg for both pressure wires and 23.3 mm Hg for the microcatheter. At a 90° position the mean pressures were respectively 36.3 mm Hg for the Volcano wire, 33.3 mm Hg for the SJM wire and 39 mm Hg for the microcatheter (Fig 5 + appendix 4). The microcatheter measurements deviated slightly from the wire measurements for the lower and higher angles. At 45° the accordance between the measure devices was good (Fig 5).

In vivo pressure measurements: pressure wires versus the microcatheter (N=10)

In the inguinal ISV, mean pressures at 0° were 7 mm Hg, 16 mm Hg and 12 mm Hg for the SJM wire, the Volcano wire and the microcatheter respectively. At 45° these results were 19 mm Hg, 25 mm Hg and 25 mm Hg. At the outflow of the ISV, mean pressures at 0° were 10 mm Hg, 15 mm Hg and 16 mm Hg for the SJM wire, the Volcano wire and microcatheter respectively. At 45° these results were 9 mm Hg, 16 mm Hg and 18 mm Hg. The SJM measurements were consistently lower than the Volcano measurements (5 to 9 mm Hg). The pressures measured with the microcatheter oscillated consistently between the results obtained by both pressure wires. The in vivo accordance between the pressure wires and the microcatheter was considered strong enough to continue the measurements with the microcatheter alone.

In vivo pressure measurements with the microcatheter (N=42)

In 42 patients (12-53 y, mean 24 y), mean pressures in the inguinal ISV were 15 ± 4 mm Hg and 23.5 ± 6 mm Hg at 0° and in 45° position respectively. At the outflow of the ISV the mean pressures were 13 ± 3 mm Hg and 13 ± 4 mm Hg at 0° and in 45° position respectively. In the RV, we measured 12 ± 3 mm Hg and 10 ± 5 mm Hg at 0° and in 45° position respectively.

Extrapolation of the pressure from 45° to 90° (N=42) (appendix 3)

The mean measured pressure of 23.5 mm Hg at 45° in the inguinal ISV would correspond with a calculated fluid column of 30.4 cm height (A on Fig 4). According the formula described above, the height at 90° would be 42.9 cm (C on Fig 4), allowing us to calculate an extrapolated hydrostatic pressure of 33.2 ± 8 mm Hg in the inguinal ISV. An increase of 10 mm Hg when we would change the position from 45° to 90° is very close to what the theoretical calculations predicted (Fig 5, but with density of blood and without the radius component).

In vivo distant measurements

From the radio-opaque yardstick we read a mean distance of 26.3 ± 3 cm between the inguinal ISV and the horizontal part of the RV. Using this distance as the height of the blood column in a 90° upright position, we can calculate a hydrostatic pressure of 20.3 mm Hg in the inguinal ISV.

The difference between the extrapolated pressure in a 90° upright position and the calculated pressure from the mean height of the blood column is therefore 33.2 - 20.3 = 12.9 mm Hg.

DISCUSSION

In this study, we demonstrated that the pressure in the inguinal ISV in standing patients with a varicocele should be 33.2 mm Hg on average. However, we also found that this intravascular pressure could not be purely hydrostatic because the calculated pressure from the "height of spermatic vein blood column" was only 20.3 mm Hg. The chasm of 12.9 mm Hg between the pressures obtained by the two different approaches can be attributed to the systemic venous pressure. This finding was confirmed by the pressure registrations in the renal vein, which varied little with position and floated around 12 mm Hg.

The systemic venous pressure is a physiological pressure of a closed vessel system, which is omnipresent and greatly independent of horizontal or erect position. As this venous pressure is about 12 mm Hg, then the arteriolar pressure in the testis should be at least 20 mm Hg to preserve a physiological arteriolar-venule gradient. In a non-varicocele situation, a certain hydrostatic pressure will be present, probably determined by the position of the lowest competent valve. Therefore, we could expect an additional 5 to 8 mm Hg physiological hydrostatic pressure. To overcome this combined venous pressure, the arteriolar pressure in the testis should be much higher than 20 mm Hg, may be at least 25 mm Hg. In other tissues, such as the base of the fingernail, pressure assessment with a micromanometer on the arterial end of the capillaries resulted in values of 30 to 40 mmHg [24]. From animal experiments, we learned that testicle capillary pressure is very low (about 10 mm Hg) and highly sensitive to an increase in venous pressure [16]. The increase in venous pressure is transmitted for more than 90% to the post capillary venules [17].

At first sight, the hydrostatic component alone is less than expected to build a pathological counter pressure against arteriolar venule gradient. However, the hydrostatic component is underestimated because we did measure in the inguinal ISV and not in the PP, which is about 10 cm lower. By applying the $P = \rho \; x \; g \; x \; h$ formula, the hydrostatic component will rise to about 28 mm Hg. Estimating that the arteriolar testicle pressure in humans is about 25 mm Hg, our results demonstrated that the arteriolar-venule pressure gradient is reversed in varicocele patients. The effect of the hydrostatic component (28 mm Hg at the PP) alone might be enough to induce flow disturbance. However, taking into account the systemic venous pressure of 12 mmHg, the reversed arteriolar-venule gradient might be as high as 15 mm Hg. This finding of a significant venous counter pressure supports the hypothesis that alterations in arterial supply impair testicle nutrition and hence spermatogenesis [25].

Similar pressure measurements in varicocele patients were performed antegrade by direct puncture of the PP. Sayfan et al. punctured the ISV and registered a mean pressure of 18.73 mm Hg in 45° semi-erect position at the inguinal ISV [20]. Extrapolating to an erect position, this pressure value increases to 26.4 mm Hg, which is lower but comparable with the pressures obtained retrograde in our study. However, as these authors found similar pressures in a non-varicocele control group, they saw no association between increased venous pressure and subfertility in varicoceles. Other investigators could detect that the hydrostatic pressure was 20 mm Hg higher in the varicocele group than in the control group [21]. However, the absolute hydrostatic pressures retrievable from both studies of this work group were inconceivably high with means of 80 mm Hg or more [21,26]. A mean hydrostatic pressure of 60 mm Hg in 30 normal ISV's is unrealistic and probably caused by a methodological error.

As expected, the arteriolar-venule pressure reversal depends on the patient's position. The hydrostatic pressure component disappears in 0° supine position but the systemic venous pressure pertains. Indeed, the measured pressure at the inguinal point of the ISV in the 0° position was consistently low (15 mm Hg) and allowed restitution of a physiological gradient. Our observation is in agreement with the results of Sayfan et al. who measured by direct antegrade cannulation a mean pressure of 11.2 mm Hg in rest.

The pressure at the outflow of the ISV in 0° supine position was more or less equal to the pressure in the inguinal ISV but, surprisingly, did not rise after 45° table inclination. Carl et al., also using retrograde catheterization, found similar results at the outflow in horizontal (11.9 mm Hg) and erect (10 mm Hg) position, albeit in 4 patients [(27)]. This observation doesn't seem in accordance with the physiology of blood circulation and blood pressure. Calculating the pressure in a vein in a standing person should take into account the height of the blood column between the vein and the right atrium, disregarding the presence of valves [(24)]. At the RV and the upper ISV the concept of hydrostatic pressure seems not applicable. Probably the presence of an incompetent outflow valve allows control of positional pressure changes. The venous system is a closed dynamic system with a pressure pump (the heart, the arteries and the musculature), which controls pressure fluctuations according to the principles of fluid dynamics.
This study found evidence that a pure hydrostatic pressure model is insufficient to explain the abnormal venous counter pressure [(28)]. The concept that the pressure in a horizontal position is zero, did not stand the experimental proof. In a supine 0° position we observed pressures in the RV and the ISV between 12 and 15 mm Hg instead of 0 mm Hg [(28)]. With correction for this systemic venous pressure, our extrapolated measurements would correlate with a fluid column of 53 cm. In a male of average height, this column would rise up far above the RV up to the right atrium. Above the RV, again systemic fluid dynamics of a closed system compensate and interfere with the hydrostatic pressure.
Our study has some limitations and shortcomings.

Firstly, we applied extrapolation to calculate the pressure at a 90° position. We used the semi-erect position (45°) propagated by Mali et al. to avoid aseptic conditions and orthostatic side effects [(23)]. Overestimation of the pressure because the kidney and the RV descend 1 to 2 cm in upright position is of low relevance as the PP might descend as well.

Secondly, although we would have liked to perform measurements at the PP level, catheter manipulations and fluoroscopic yardstick measurements between the inguinal ISV and the PP were not possible because of the radio-protective testis shielding.

Thirdly, unlike the study of Shafik, we are not able to perform post treatment pressure measurements since the glue in the ISV precluded retrograde catheterization. The only way to measure pressure post-embolization is by direct puncture of the PP. The decrease of venous pressure post treatment as shown by Shafik et al. needs further confirmation by a study that utilizes an optimized technique for needle pressure measurements at the PP [(26)].

Fourthly, the proposed physiological arteriolar testicular pressure in humans of about 25 mm Hg is a calculated estimation. This pressure is fixed somewhat arbitrarily, based on venous pressure of at least 20 mmHg (systemic venous and hydrostatic pressure according lowest competent valve) and the assumption that in the testis arteriolar pressure is lower than in other organs [(16)]. Control experimental data on arteriolar or venular pressures in the human testis are not available.

A major shortcoming of our study is that we have no control group of patients without a varicocele. Pressure measurements in control groups are rare and inconsistent [(20)] [(21)]. We can

expect a hydrostatic pressure component in normal spermatic veins as well. Apart from the possible ethical conflict with catheterization of healthy persons, it will be challenging to perform a retrograde distal catheterization because of the competent valves.

Nevertheless our study was performed under standardized and controlled conditions in a large cohort of varicocele patients. The technique of retrograde catheterization and pressure measurements was double checked and fine-tuned by in vitro and in vivo experiments, securing correct and reproducible pressure data. Hydrostatic pressures were determined by two independent techniques, one starting from pressure registrations and one based on the height measurements. Both methods were consistent in delineating the hydrostatic pressure component in varicoceles.

Our study of pressure measurements could be a start for analyzing and determining the role of hydrostatic pressure in various clinical varicocele manifestations. We think of childhood varicocele presenting with or without testicular hypotrophy, adult varicocele with and without subfertility. In all subtypes, pressure measurements could not only contribute in better understanding of the pathophysiology, but could also be utilized in decision making whether to treat or not.

CONCLUSION

In a standing patient with varicocele, the intravascular pressure in the inguinal ISV is elevated and consists of a hydrostatic (20 mm Hg) and systemic venous component (12 mmHg). This venous counter pressure could impair arterial supply and spermatogenesis in varicoceles, but to what extent and in which situation is unknown. The paradigm can only be unraveled by standardized pressure studies in a normal control group. Then we will finally be able to answer whether erect posture in varicocele patients leads to infertility.

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5. General discussion and conclusion

General discussion and conclusion

Part 1 Endovascular treatment of varicocele with viscous liquid embolic agents

1.1 Efficacy and safety of two different n-butyl-2-cyanoacrylates for the embolization of varicoceles: a prospective, randomized, blinded study and

1.2 Tolerance of glue embolization under local anesthesia in varicoceles: A comparative study of two different cyanoacrylates.

It is widely known that endovascular embolization of varicoceles has a very low complication rate (<1 %) in comparison with many of the surgical options.
Non-liquid embolic agents such as metallic coils and detachable balloons or low viscosity liquids such as sclerosing agents, are deliberately used by interventional radiologists.
Metallic coils have the same disadvantage as surgical clips. With these materials it is difficult or impossible to occlude all collateral connections with the ISV. When collaterals remain patent, reflux may persist and recurrences may occur.

Sclerosing agents can penetrate into these connections, if they are injected with a proper technique. Because sclerosing agents are not radio-opake and have a low viscosity, the extension of the embolization is not always controllable and the risk of non-target embolization is substantial.
High viscosity liquids such as cyanoacrylates induce an intravascular adhesive polymerization with a permanent occlusive effect. This glue can be mixed with Lipiodol for radio-opacity as well as to change the polymerization rate. Confidence in this type of gluing embolic agent has been very high at our department of Interventional Radiology: it has been used for more than 30 years in the treatment of varicoceles.

There are currently two commercially available tissue-adhesives that can be used for the embolization of varicoceles. The two adhesives differ only minimally in chemical formula, but polymerize in a different way. The more recently developed Glubran2, available since 2001, would have the same occlusion features as the older glue, hystoacryl transparent. The manufacture of Glubran2 obtained a CE label for intravascular use and alleged that Glubran2 has a higher stability and a lower toxicity.

We tested both glues (Histoacryl transparent, Glubran2) for differences in efficacy, safety and tolerance in a double-blind, prospective, randomized study (aim 3). We found that both glues can be handled in the same way and that the embolic result is similar.
Technical success was 100%, this means that in all patients we could effectively block the reflux in the insufficient ISV. The procedure was very safe with no complications caused by the glue.
Concerning patients comfort we were the first to delineate a late inflammatory reaction to the cyanoacrylates. During the week after embolization, 59% of patients reported some discomfort, which was in 35% at least a bearable pain.

There was no significant difference in discomfort between the two glues in the post-embolization week (aim 4). Moreover, there was some mild acute inflammatory pain reaction during the embolization in 20% of the patients. There was no difference between both glue groups.
Given these findings, patients should be informed that they might experience discomfort or mild pain during and after embolization of their varicocele. As this inflammatory reaction is self-limiting and mostly mild, we would not advise to prescribe NSAIDs prophylactically.

Because there is no difference between Histoacryl transparent and Glubran2, both glues can be used effectively and safely. However it is medicolegally sensible to choose Glubran2 because it has a CE approval for endovascular use.

1.3 Varicocele embolization with Onyx: a feasibility study

Embolization with glue, as described in the previous section, is an efficient and safe method to treat varicoceles. We demonstrated that the injection of glue in the ISV might cause discomfort and mild pain, particularly in the post-embolization period.
Although technical success rate of glue embolization is very high, the interventionalist might encounter anatomical situations in which the penetration of glue is less satisfactorily.

Another liquid embolic agent, which is non-adhesive, is ethylene-vinyl alcohol also called "Onyx". Onyx is a plastic dissolved in dimethyl sulfoxide. After diffusion of the solvent, Onyx solidifies to a rigid cast, which can be pushed and extended in different directions.
For these reasons, Onyx embolization has become the primary intravascular therapy for cerebral arterio-venous malformations (c-AVM) and dural fistulas (d-AVF). Because of the anatomical similarities between AVM and complex insufficient ISV, we thought that Onyx could be a potential embolic agent in complex varicoceles. Moreover, we know from extirpated AVM species that Onyx does not induce a post-embolization inflammatory reaction.
In a pilot study we tested Onyx as an embolic agent in ISV embolization (aim 5). We found that Onyx was efficient and indeed better tolerated in the post-embolization period. However, there was an acute pain reaction during the injection of Onyx in 9 of 10 patients, prompting to stop the injection temporarily in 6 patients. The technique to inject Onyx as we do with glue, allowing only little reflux, demonstrated to be suboptimal and ensued a higher radiation dose. Further research should concentrate on adaptation of the embolization technique as used for c-AVM and on reducing the acute pain reaction by injection of intravenous anesthetics.

1.4 Radiation exposure related to the fluoroscopy guided embolization of varicocele

The first basic principle of radiation protection is “justification”. This means that the clinical benefit of the treatment has to outweigh the possible radiation-induced risks. The treatment of varicoceles to prevent infertility or to improve fertility, is very controversial. Other studies and our study, show that the gonadal dose in varicocele embolizations is definitely far below the lower threshold corresponding to the deterministic effect of temporary sterility (150 mSv).

Based on the in-vivo measured testes doses, we could estimate the risks of hereditary effects as being very low (mean value of $3,5\ 10^{-6}$). With respect to the risk of cancer mortality a mean value of 0,06 % was calculated. The latter value is much lower than other typical interventional X-ray

procedures (aim 6). According to the NCRP publication 168, the obtained risks in our study population are requiring a "minor to moderate benefit" to justify the varicocele embolization procedure. The low dose and risk values obtained are probably linked to a set of specific radiation reducing measures. The latter optimization includes the use of pulsed fluoroscopy, the application of gonadal shielding and the careful collimation of the radiation beam.

Apart from the patient, the interventional radiologists are also at risk, especially those, which perform a high amount of procedures. Optimizing patient radiation exposure, will also reduce the patients scatter dose and hence the staff dose.

Part 2 Anatomical phlebographic aspects and fluid dynamics in varicoceles

2.1 Internal spermatic vein insufficiency in varicoceles: a different entity in adults and adolescents?

In everyday practice, varicoceles are treated because of symptomatology (pain and congestion at the scrotum) and the assumed association with infertility. In adolescents, varicoceles are mostly asymptomatic. Treatment of adolescent varicocele is advised to anticipate testicular hypotrophy and future fertility. To justify this prophylactic treatment, it is generally assumed that varicocele in children are an early stage of the varicocele in adults. Although the adult varicocele is usually symptomatic, treatment is requested in first place because of sperm dysfunction.

At a certain moment in my practice, I had the impression that the embolization of a varicocele in a child seemed a technically less challenging procedure than in an adult. I thought that "the easier procedure" was due to the absence of competent valves and a more straight anatomy in adolescents. These observations could point at a different phlebographic anatomy between adolescents and adults, and indirectly disclose a different pathophysiology of varicoceles (aim 8).

To investigate this hypothesis, we set up a retrospective study to compare phlebographic radio-anatomical landmarks between adolescents and adults (aim 7). For this purpose, we used the selective phlebographies that were performed prior to the embolization of the varicocele.
After analysis and comparison of about 500 phlebograms, we demonstrated that our suspicion was not unfounded. Adults had significantly more often a competent outflow valve than adolescents. Moreover, adult varicocele had a more complex anatomy consisting of a significantly higher number of collaterals and of a complex outflow in the renal vein. The phlebographic complexity of adult varicocele could be the remnant of an insufficient embryonic venous drainage during the ontogenesis of the left ISV.
Left-sided varicocele in many adolescents seems to be more a congenital abnormality rather than a progressive chronic disease: we found a higher rate of insufficient outflow valves, congenital renospermatic bypasses and the compressive nutcracker phenomenon.

On the other hand, we have arguments that right-sided varicocele might be a progressive disease. The incidence of an insufficient ISV increase with age (2.4 times more often in adults (33%) than

in adolescents (14.7%). The diameter of the ISV also increases significantly with age: a fact that could point at a degenerative process with reflux and dilatation.

2.2 Internal spermatic vein pressure measurements in varicoceles: does erect posture in varicoceles lead to infertility?

Many theories have been developed about how varicoceles can cause infertility. The causal association is most probably multifactorial, combining of lifestyle factors, genetic factors and the effect of reflux of blood into the PP.

The reflux of blood into the ISV is a direct result of the insufficiency of valves, a mechanism that we can observe during the phlebography of varicocele patients. By reflux of warm blood, temperature in the testicle rises. Furthermore, in a varicocele patient standing upright, the hydrostatic pressure at the PP and the testicle increases according the height of the fluid column in the ISV. Venous drainage at the PP will then be impaired, and the cooling of the testicle less efficient. This hydrostatic "counterpressure" might interfere with the arterial and nutritional supply of the testicle and decrease spermatogenesis and testicle growth.

In an editorial of Andrologia, Gat titled that " Erect posture of humans leads to infertility. " [(1)]. In 2 other articles, he described that the increased pressure at the PP is only caused by the height of the blood column in the insufficient ISV. He calculated this hydrostatic pressure by the expected distance between PP and renal vein according the formula $P = h \times g \times \rho$, resulting in a value of 31.5 mm Hg at the left and a value of 27 mm Hg at the right side. This hydrostatic pressure is, according to Gat, high enough to cause testicular insufficiency and infertility in varicoceles. This is the theoretical point of view.

Pressure measurements in the PP or inguinal ISV of varicocele patients were previously performed by direct measurements through a needle or catheter in the PP [(2-4)]. The pressures that were measured in these studies were inconsistent and conflicting, in our opinion because of methodological errors.

Interested in the concept, and critical to a hypothesis that was not tested on the field, we aimed to measure pressures in the caudal ISV directly and to find out whether infertility can be explained by increased pressure (aim 10).

We soon understood that performing pressure measurements through a microcatheter in the ISV was not an easy task. Initial results were not at all consistent. We had to test and calibrate our method ex-vivo and to standardize the measurement method. We compared pressures obtained via a microcatheter (external pressure transducer) with those registered with two different commercial pressure wires (aim 9). In-vitro (in an experimental tube) and in-vivo (endovascular in the ISV) tests demonstrated that the direct measurements (pressure wires) could be reproduced by the microcatheter measurements (external pressure transducer).

For the first time, an in-vivo experiment done in 42 patients showed that the absolute mean pressure in the inguinal left ISV is 33 mm Hg.
According to the hypothesis of Gat, this pressure would only exist of a hydrostatic pressure component. However, the height of the blood column that produces this hydrostatic pressure

would reach far above the renal vein, even higher than the right atrium. We disclosed that the pressure in the renal vein and at the outflow of the ISV did not change with patient's position. It was constant at about 12 mm Hg, corresponding to the systemic venous pressure. The absolute measured pressure is therefore composed of a hydrostatic (21 mm Hg), and a systemic pressure (12 mm Hg) component. This hydrostatic pressure was compatible with the indirect calculation from the measured height of the ISV (distance between inguinal ISV and renal vein).
As the normal capillary pressure of the testicle can be estimated at less than 20 mm Hg, then the hydrostatic pressure in upright standing position alone appears to be high enough to act as a counterpressure. This counterpressure could impair arterial supply and spermatogenesis in varicoceles.

Only standardized pressure measurements in fertile patients without varicoceles would be able to answer whether erect posture in varicocele patients leads to infertility.

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General conclusion and perspectives

In the first part of this work, we have demonstrated in a randomized controlled trial that the current commercially available tissue-adhesives, Histoacryl transparent and Glubran2, are equally efficient and safe for transcatheter embolization of varicoceles.

Tissue-adhesives or glue can cause a mild, self-limiting pain in 1/3 of the patients in the week after embolization, independently of what product was used. Whether this inflammatory pain occurs in certain patients, is related to a special phlebographic anatomy or can be treated prophylactically with a NSAID can be subject of a next study.
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Because Glubran2 has a CE label for intravascular use, it is medico-legal justified to use this glue. Worldwide, glue is not a popular embolic agent for the treatment of varicoceles, probably because it requires more skills or preconception persists about the potential complications. Controlled randomized trials, reporting the success and complications rate, as well as the pregnancy rate could lead to an FDA approval for intravascular use and contribute to the attractiveness of glue.

In a feasibility pilot study, we demonstrated that Onyx has the potential of an efficient and safe agent for the embolization of varicoceles. In contrast to glue, the pain reaction in the week after

embolization is not an issue. Unfortunately, the acute pain reaction as well as the radiation exposure during embolization have to find a solution before Onyx can be recommended.

Local injection of an anesthetic in the ISV at the site of planned Onyx injection should be tested in a next pilot study. By avoiding the pain reaction, the intervention will run more smoothly and straight-forward, reducing the fluoroscopy time and number of acquisitions. Finally, we have to explore in which anatomical situation Onyx can constitute an advantage over the other embolics.

Our prospective study proved that the radiation exposure is safe during embolizations of varicoceles with highly viscous liquid products. We report a gonadal dose that is far below the lower threshold corresponding to the deterministic effect of temporary sterility (150 mSv). We could estimate the risks of hereditary effects and the risk of cancer mortality as being very low and much lower than other typical interventional radiographic and or fluoroscopic procedures. According to the NCRP publication 168, the obtained risks in our study population are requiring a "minor to moderate benefit" to justify the varicocele embolization procedure. The low dose and risk values obtained are probably linked to the use of pulsed fluoroscopy, the application of gonadal shielding and the careful collimation of the radiation beam. Optimizing patient radiation exposure, will also reduce the patients scatter dose. Apart from the patient, the interventional radiologists are also at risk, especially those, which perform a high amount of procedures. In future, by the use of the flat panel detectors, the radiation exposure may be reduced even further.

In the second part of this work, we delivered a contribution to the ontogenesis and pathophysiology of varicoceles. We have demonstrated that in left-sided varicocele children's spermatic vein showed more often valve insufficiency, renospermatic bypasses and nutcracker syndrome. In adults, reflux more often is caused by collateral connections. Left varicocele seems rather a congenital abnormality than an evolutionary disease as commonly believed.
At the right varicocele, we have shown that the diameter of the ISV increases in adults and that a bilateral varicocele occurs 2.4 times more. As far as the right varicocele is concerned, we do have arguments for an evolutionary chronic disease.

In a subsequent study, we could check whether phlebographic landmarks are correlated with clinical presentation, semen analysis, thermography or color Doppler ultrasound. We would like to find out whether adults consulting for infertility have i.e. more an "adolescent-like" phlebography with incompetent valves. Or, is there an association between phlebographic competent valves and pure discomfort (no fertility issue)? Such links might predict whether certain children may profit from a prophylactic embolization, or might form an algorithm for treatment indication.

We also made a contribution in the controversial topic that associates varicoceles with infertility. We designed a standardized, inexpensive and reliable method for pressure measurements in the ISV. We demonstrated in-vivo that the mean absolute pressure in the inguinal ISV in the upright position is significantly high enough to build a counter pressure to the capillary pressure, and hence impair the spermatogenesis.
In addition, we have invalidated Gat's hypothesis and proven that not only the hydrostatic pressure is responsible for this elevated pressure, but the sum of the systemic and the hydrostatic pressure.

Our method of intravenous pressure measurement can be used for future research in hydrodynamics of the spermatic vein and veins in general. We could investigate whether clinical presentation, thermography, CDUS, phlebographic anatomy or age are associated with different pressure levels. Here again, the detection of certain sub-groups could change the therapy policy.

However, we still ignore whether the pressures we obtained, are “really” pathological since we can not compare with a healthy control population. We could measure the pressure in the ISV of a control group of fertile men without varicocele. It will not be an easy task to convince the ethics committee. Moreover, it will be a technical challenge to catheterize healthy men retrograde through several competent valves down to the inguinal ISV. Or we could imitate the situation of a normal man, by temporarily closing the ISV with a balloon in varicocele patients and measure the pressure distally to the balloon.
Only then we could answer the question " does erect posture in varicoceles lead to infertility?"

6. Summary

Summary

In the first part of this work we have demonstrated that the endovascular treatment of varicoceles with glue is an efficient, safe and tolerable method. We showed that the current commercially available adhesives, Histoacryl transparent and Glubran2, do not differ with regard to efficiency and safety during embolization of varicoceles.
We were the first to demonstrate that both glues cause a mild pain in 30 % of the patients in the week after embolization. Glubran2 is medico-legal justified to use because it has a CE label for intravascular application. The advantages of glue for the endovascular treatment of varicoceles is at the moment underestimated because the use of glue lacks well-constructed studies and an FDA approval for intravascular use.

We were the first to demonstrate the feasibility and safety of Onyx for the embolization of varicoceles. The pain reaction in the week after embolization is negligible compared with tissue adhesives. The acute pain reaction and the radiation exposure during embolization precluded currently its use. Intravascular local anesthesia before embolization and change the embolization technique could solve these disadvantages.
We are convinced that Onyx will have its indications in the treatment of varicoceles.

Our prospective study proved that the radiation exposure is safe during embolizations of varicoceles with highly viscous liquid products. The gonadal dose is low and the risks of hereditary effects and the risk of cancer mortality has been very low and much lower than other interventional radiographic and or fluoroscopic procedures. The low dose and risk values obtained are probably linked to the use of pulsed fluoroscopy, the application of gonadal shielding and the careful collimation of the radiation beam.

In the second part of this work, we delivered contributions to the research in the pathophysiology of varicoceles and its' association with infertility. As the first, we demonstrated anatomical differences between adults and adolescents. We showed in the left varicocele, insufficiency of the ISV could be explained more by a congenital abnormality (in adolescents) or ontogenetic failure in venous development (in adults) than by an evolutionary process. In right varicocele, we do have arguments for an evolutionary chronic disease.

Secondly, we designed a standardized and reproducible method for pressure measurement in the ISV. We demonstrated that the mean absolute pressure in the inguinal ISV in the upright position is higher than the veno-capillary pressure in the testicle. In addition, we have invalidated the theoretical hypothesis of “a pure hydrostatic pressure model” and we proved that the absolute pressure in the lower ISV is composed of the systemic pressure and the hydrostatic pressure.
Only comparable pressure measurements in a control group of fertile male without varicocele could answer the question "does erect posture in varicoceles lead to infertility?"

Samenvatting

In het eerste deel van dit werk hebben we aangetoond dat de intraveneuze behandeling van varicoceles met weefsel klevers een efficiënte, veilige en aanvaardbare methode is. We toonden aan dat de huidige verkrijgbare lijmen, Histoacryl transparant en Glubran2, niet van elkaar verschillen wat efficiëntie en veiligheid betreft tijdens embolisatie van varicoceles.
Wij waren de eersten om aan te tonen dat beide lijmen een milde pijn in 30% van de patiënten in de week na embolisatie kan veroorzaken. Het is medico-legaal gerechtvaardigd om Glubran2 te gebruiken omdat het een CE-label heeft voor intravasculaire toepassing. Het voordeel van lijm voor de behandeling van varicoceles is op dit moment niet erkend omdat goed geconstrueerde studies en een FDA goedkeuring voor intravasculair gebruik ontbreken.

Wij waren de eersten om de haalbaarheid en de veiligheid van Onyx voor de embolisatie van varicoceles aan te tonen. De pijnreactie in de week na embolisatie is verwaarloosbaar in vergelijking met weefsel klevers. De acute pijnreactie en de stralingsbelasting tijdens embolisatie vormen momenteel een probleem voor het routine gebruik van Onyx. Intravasculaire injectie van een anestheticum en het gebruik van een andere embolisatie techniek kunnen deze nadelen oplossen
Wij zijn ervan overtuigd dat Onyx zeker een toekomst in de behandeling van varicoceles zal hebben.

Onze prospectieve studie bewees dat de stralingsblootstelling tijdens embolisaties van varicoceles met zeer viskeuze vloeibare producten veilig is. De gonadale dosis is laag en de risico's van erfelijke effecten en het risico van kankersterfte is zeer laag en veel lager dan bij andere interventionele radiografische en fluoroscopische procedures. De lage dosis en risicowaarden zijn waarschijnlijk gekoppeld aan het gebruik van gepulseerde fluoroscopie, de toepassing van gonadale afscherming en de zorgvuldige collimatie van de stralingsbundel.

In het tweede deel van dit werk hebben wij bijgedragen aan het verdere onderzoek van de pathofysiologie van varicoceles en zijn verband met onvruchtbaarheid. Als eersten toonden we sommige anatomische verschillen tussen volwassenen en adolescenten aan. We toonden in de linker varicocele, dat de insufficiëntie in adolescenten en volwassenen meer kan worden verklaard door een aangeboren afwijking dan door een evolutionaire ziekte. Wat de rechter varicocele betreft, hebben wij argumenten voor een evolutionaire chronische ziekte.

We waren de eerste om een gestandaardiseerde en betrouwbare drukmeetmethode voor de ISV te ontwikkelen. Wij hebben als eersten aangetoond dat de gemiddelde absolute druk in de inguinale ISV in rechtopstaande positie hoger is dan de veno-capillaire druk in de testis.

Bovendien hebben we de theoretische hypothese van “een zuiver hydrostatisch druk model “ ontkracht en hebben we bewezen dat de absolute druk samengesteld is uit de systemische druk en de hydrostatische druk.
Alleen vergelijkbare drukmetingen in een controlegroep van vruchtbare mannen zonder varicocele zouden een antwoord kunnen geven op volgende vraag "leidt rechtstaande houding in de varicoceles tot onvruchtbaarheid?"

Sommaire

Dans la première partie de cette étude, nous avons démontré que le traitement intraveineux de la varicocèle par la méthode colle est efficace, sécuritaire et acceptable. Nous avons démontré que les colles actuellement disponibles, soit l'Histoacryl transparente et le Glubran2, ne diffèrent pas en termes d'efficacité et de sécurité au cours de l'embolisation de varicocèle.

Nous étions les premiers à démontrer que les deux colles peuvent provoquer une légère douleur chez 30 % des patients dans la semaine qui suit l'embolisation.

D'un point de vue médico-légal, il est justifié d'utiliser Glubran2 vu que ce dernier possède d'un label CE pour l'application intravasculaire. La supériorité de l'adhésif pour le traitement de la varicocèle n'est actuellement pas reconnue par manque d'études bien-construites au niveau de l'utilisation de la colle et par manque de l'approbation de la FDA pour les applications intravasculaires.

Nous étions également les premiers à démontrer la faisabilité et la sécurité de Onyx pour l'embolisation de la varicocèle. La douleur réactive au cours de la semaine après l'embolisation est négligeable par rapport aux colles tissulaires. La réaction de douleur aiguë et l'exposition aux rayonnements lors de l'embolisation sont actuellement un problème pour une utilisation de routine. L'application de l'anesthesie locale, intravasculaire avant l' embolisation et employer une autre technique de l'embolisation peut donner une solution. Nous sommes convaincus que Onyx aura certainement un avenir dans le traitement de la varicocèle.

Notre étude prospective a prouvé que l'exposition aux rayonnements pendant les embolisations de varicocèle avec les produits liquides très visqueux est sécuritaire.

La dose gonadique est faible et les risques d'effets héréditaires ainsi que le risque de mortalité à cause d'un cancer est très faible et nettement plus faible par rapport à d'autres procédures de radiographie et fluoroscopie interventionnelle. La faible dose et les valeurs de risques sont probablement liées à l'utilisation de la fluoroscopie pulsée, l'application de protection des gonades et à la collimation prudente de rayonnement du faisceau.

Dans la deuxième partie de ce travail, nous avons contribué à la recherche de la physiopathologie des varicocèles et son lien avec l'infertilité. Nous étions les premiers à démontrer certaines différences anatomiques entre les adultes et les adolescents.

Nous avons démontré dans la varicocèle gauche, que l'insuffisance chez les adolescents et les adultes peut s'expliquer plus par une malformation congenital que par une maladie évolutive.

En ce qui concerne la varicocèle droite, nous avons des arguments pour une maladie chronique évolutive.

Nous étions les premiers à développer une méthode de mesure de pression pour la ISV standardisée et fiable. Nous étions les premiers à démontrer que la pression moyenne absolue à la ISV inguinale en position verticale est supérieure à la pression veino-capillaire dans les testicules.

En outre, nous avons contredit la théorie hypothétique d'un modèle uniquement de la pression hydrostatique et nous avons prouvé que la pression absolue est composée de la pression

systémique et de la pression hydrostatique.

Seul des mesures de pression comparables d'un groupe témoin d'hommes fertiles sans varicocèle serait en mesure de répondre à la question « est-ce que une position érigée dans la varicocèle conduit à la stérilité ? »

7. List of Abbreviations

List of Abbreviations

ISV: interal spermtic vein

PP: pampiniform plexus

RV: renal vein

c-AVM: cerebral arteriovenous malformation

d-AVF: dural arteriovenous fistula

8. List of Publications

List of Publications

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9. Acknowledgements

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This work would never have been accomplished without the influence of various factors. If one chooses at first to acquire clinical experience with however the desire to write an PhD sometime in the future, then this implies a number of essential conditions and human interventions in order to realize this, the one condition even more scientific than the other... Therefore my acknowledgments match perfectly with the following brief manual:

"How to write A PhD at mature age for dummies!"

First: During your student years you should not have taken the studies and life itself too seriously. The more you have tasted of all nightly sins and challenges in the party scene, the easier it is many years later, to put all pleasures temporary aside in order to concentrate for a 100% on your Phd. Hence I want to express my thanks to all nightly companions (....) who never pointed out to me that there were lessons scheduled the next day and that we actually had to study. Fortunately, there were also more serious friends, who together with my parents provided some counterbalance.

Secondly, a starting interventional radiologist has to be able to appropriate a specific domain amongst the bulk of daily interventions. Preferably you choose a domain in which you have autocracy and in which you can become a real expert. A " chief " who is not interested in the chosen domain or who grants you total freedom in order to explore your domain is a condition sine qua non. Fortune was again at my side since my promoter combined both qualities.

Then I was fortunate that thanks to the work of Professor Kunnen, the procedure of embolization of varicoceles was already established in the UZ Ghent. Thanks to most referrers who stayed faithful to me, my expertise kept on growing.

Once you have acquired the expertise after years of hard work, the most interesting part of the job as a clinical scientist starts, namely the experiments on patients or the set-up of studies, randomized or non-randomized but all provided with a well prepared informed consent and of course with the blessing of the Ethical Committee.
I will never forget the all saying look of my nurse when I told the patient - after he had put his signature on the informed consent that it was possible that after the embolization with Onyx, he could possibly spread a rather unpleasant smell causing some nuisance for his neighbors. Therefore I want to express my gratitude to all patients of East and West-Flanders because without them, there would not have been any result or conclusion.

And before you realize it, you're combining several studies and you have to conclude that you need lots more time in order to process and manage everything. Fortunately, I could always count on the study nurses, nurses and secretaries. A lot of them came, stayed for a while and then left, few of them stayed until their retirement and a few amongst them are fortunately still enjoying the work. All of them contributed to this PhD, thank you Jolien, Ellen en Lynn, Stefaan, Chris, Roos, Dirk, Tom, Patrick, Olivier, Martin, Jan, Freya, Nancy (†), Ann, Joke, Heidi, Julie, Dieter, Murat, Jan, Esther, Nathalie, Adriano, Ruth, Gylaine (†), Isabelle, Denise, Joke and Magalie.

Unfortunately, working on Vinrad as interventional radiologist is not really associated with many free moments and the processing of studies and the writing of the results went too slowly forward. Everything had to happen between 'the carpaccio and the asparaguses'. Then it is crucial that amateurism is converted into professionalism and that real time is provided for your research. Thanks to Professor Colardyn (managing director at that moment) and the lobbying of again my promoter, I was able to compete for the KOF (Clinical Research Fund) grant of the UZGent. This scholarship allowed me to replace my clinical work part-time during four years, by a colleague interventional radiologist. Thanks for my Dutch friends and former residents on Vinrad, Emile and Alex.

Unfortunately, those 4 years were several times interrupted by practical problems and setbacks in the Vinrad-team, so that the study itself took a year longer than scheduled. At such a time you have to be able to rely on a superior who works again more in the operating rooms (even causing his dosimeter to rise above the allowed value) and of course on colleagues, consultants and assistants who were always willing to do the work and only disturbing you if really necessary. Thank you Katrien, Elisabeth, Frans, Olivier, Rob, Philip, Philip, Johan, Tom, Sven, Niels, Jeroen, Stephanie, Eva and Pieter. Also thanks to Sofie and Wouter, former medical students, for their excellent master thesis work on the anatomy and embryology of varicoceles.

A strong family bond without envy and bickering and with traditional periodic parties is surely an essential requirement for the success of a project.
Dear family, and godchildren, thanks for your understanding and tolerance for the fact that I was always late on your parties or sometimes even did not come at all. Believe me, it was just for this purpose. But now the work is done, I am ready to go for it again. Thanks mum and dad, Jef & Dora, Veerle, Jan, Frank, Rik, Tine, Muy-Ling, Gieles, Amber, Myrthe, Ewoud, Ella, Ibo, Silas, Arthur, Christophe, Emma, Mathis, Elena, Manu, Kristin and Dimi.
Dear Sim, Cas, Ko and Lie, I realize only too well that I neglected you all a bit during these recent years, but I promise you, better times will come (although more strict).

Good neighbors are also essential, neighbors who spontaneously pruned the hedge that I neglected due to time constraints. Thanks, Mark and Joost, Hildegarde and Evelien.

Of course, you also have be able to rely on a multitude of friends who maintain annual traditions at which you can look forward to and who make that you return fully charged (at least with some traditions and after several days), and to start all over again with a clear head. Hereby I think of the unforgettable 'Surf and kite trips', 'the Saint Nicholas Tignes short ski', ' the tasty four seasons dinners', 'the dirty gang city trips',' the exclusive off-shore ski trips'," 'the family skiing holidays', 'the extreme mountain bike trip' and' the West Flemish super col tour'. Working on my PhD, I had to skip some of the trips a few times. For most of them, I made during these last years little effort for the organization. I hereby promise improvement. Thanks Jan & Suzy, Dirk & Inge, Hendrik, Peter & Inge, Jan, Thomas, Simon, Sven & Ilse, Patrick, Philip, Jean, Patrick, Jurgen, Jorgen, Yves, Christophe, Bart, Henk, Georges, Glenn, Ann, Anneke, Frank, Dirk & Hilde, Tom...

Also my sculpting training in the Offerlaan in Ghent was really welcome and has kept me sharp during this intense period. Striking was the similarities in the interesting discussions and critical notes of Maen, Guy and Ludo (†) and of my promoter, although on a totally different subject and

in a totally different environment. Thanks for this, thanks also to all other fellow students, most of which I forgot their name.

I would also like to thank the members of the jury for their time and encouragement.
To finish, there are ultimately two persons really essential to bring this masterpiece to conclusion:

First, choose the right promoter; you need a promoter who is always willing to make time both during as after working hours, and not only when everything goes smoothly, but also when he passes through turbulent and difficult professional or family moments. I will never forget he brainstorming sessions at the NH Belfort Hotel, the discussions and philosophical reveries about varicoceles in 'Clochard de luxe', 'Martino', 'Borsalino' and all the other restaurants in Ghent still serving food after 23:00. In addition to my already advanced knowledge of cocktails, I learned to appreciate different types of Gin and tonic (in those days it was still affordable).
I also learned that a publication is only ready after it has been rewritten at least 15 times and that they always improve after each refusal. The promoter must also remain critical at all times, and has to be able to convince you that only the best is good enough. Luc, I want to express my incredible gratitude and appreciation for all your efforts.

Secondly, choose the right partner. My dearest Anne-Rose, the last three years I've put you seriously to the test with this doctorate. I vividly remember the times when I closed the door behind me for yet another evening or weekend in the UZ when I heard in the background "fucking doctorate". I realize only too well that it was not all fun with four teenagers. Luckily you had a lot of support from your parents.
Sorry for the many broken nights, if it was not by an emergency intervention then it was by working too late on this PhD and consequently falling asleep downstairs. Thanks to help me with your excellent linguistic knowledge to translate the publications and the PhD book.
Your comment that through my frequent absences I had the perfect alibi to have a mistress was certainly justified, unfortunately she was not of flesh and blood but only of letters, numbers and statistics ....
To be together with you is for me the greatest happiness and I am therefore very grateful that you sustained this period and that you spoiled me not only culinary but also in other ways, regardless of the time of my homecoming. Now there are really better times ahead of us! Thanks a lot for your support.

Life itself also needs to be favorable. Fate has tested me already a few times during my nightly journeys with the motorcycle or with the Smart to the Hospital or on the way back to home, but has always protected me until now despite the countless nights with too little sleep.

Finally, I want to thank all the friends that I'm forgetting here now, but that I will definitely remember again tomorrow.

Believe me, this is the fastest and the cheapest way ever, to treat a varicocele

I may be not totally perfect, but parts of me are excellent
(Ashleigh Brilliant)